ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL INSTITUTES OF HEALTH

1960

DIVISION OF BIOLOGICS STANDARDS
DIVISION OF GENERAL MEDICAL SCIENCES
DIVISION OF RESEARCH GRANTS
DIVISION OF RESEARCH SERVICES

NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

United States. National Institutes of Health.

ANNUAL REPORT OF PROGRAM ACTIVITIES

Division of Biologics Standards

January - December 1960

RA
401
U5645
1960

TABLE OF CONTENTS

ANNUAL REPORT

DIVISION OF BIOLOGICS STANDARDS

	DBS
Director, DBS - Summary	S
Office of the Director	1
Laboratory of Control Activities	
A - Office of Chief	2
B - Control Testing and Investigations Related to Control of Biological Products	3
C - Section on Pyrogens	4
D - Investigations Related to Establishment and Maintenance of Reference Standards for Biological Products	5
Laboratory of Bacterial Products	
A - Pertussis Vaccine	6
B - Typhoid Vaccine	7
C - Participation in Establishment of Pakistan-SEATO Cholera Research Laboratory and Conference on Cholera	8
D - Study of Cholera and other Vibrios Isolated in Bangkok 1959-60	9
E - Re-evaluation of Requirements for Cholera Vaccine	10
F - Urinary Blood Group Substance	11
G - Studies on the Specificityof Tuberculins	12
H - The Schick Test Toxin (Diptheria)	13
I - Pleuropneumonia-like Organisms from Tissue Culture	14
J - Staphylococcal Products	15
Laboratory of Viral Immunology	
A - Functions Associated with the Poliomyelitis Vaccine Safety Testing Program	16
B - Monkey Safety Test for Polilmyelitis Vaccine and Adenovirus Vaccine	17
C - The Tissue Culture Preparation and Tissue Culture Testing of Killed Virus Vaccines	18

D - The Measurement of Antipoliovirus Antibodies by the Metabolic Inhibition Test (MIT). 19
E - The Antigenic Potency of Poliomyelitis Vaccine as Determined in Chicks and in Monkeys 20
F - Study of Immunity to Poliovirus and other Virus Infections 21
G - Experimental Studies with Viruses and Cell Cultures 22
H - Studies of Neurovirulence of the Attenuated Poliovirus Strains in Monkeys 23
I - The Pathogenesis of Infectious Diseases 24
J - Experimental Studies with Cell Cultures 25
K - Biological Properties of Ribonucleic Acid from Virulent and Attenuated Polioviruses 26
L - Studies on the Vacuolating Agent 27
M - Investigation of Antigenic Variation and Neutralization of Herpes Virus 28
N - Serological Characterization of some 1960 Strains of Bovine Influenza Virus 29
O - Application of the MIT for Titrations of Viruses other than Poliovirus 30
P - Development of New Electronically Controlled Automatic Diluting Machine 31

Laboratory of Virology and Rickettsiology

A - General Aspects of Virology and Rickettsiology 32
B - Growth and Metabolism of Rickettsiae 33
C - Typhus Vaccine - living attenuated Strain E 34
D - Investigations Concerning Measles Virus and Vaccine 35
E - Investigations Concerning the Spotted Fever Group of Rickettsiae 36
F - Investigations Concerning Vacuolating Virus (VV) 37
G - Investigations Concerning Lymphocytic Choriomeningitis (LCM) Virus 38
H - Investigations Concerning Mumps Virus 39
I - Investigations Concerned with Human Hepatitis Virus 40
J - Vacuolating Virus: Pathogenicity for Man 41
K - Typhus Vaccine: Killed Epidemic 42
L - Study of Measles Virus and Serologic Response of Experimental Animals to Measles Virus Propagated in Tissue Culture 43
M - Studies on Photodynamic Resistence in Cell Cultures 44
N - The Etiology of the Sarcomas Associated with the Cyst walls of Cysticercus fasciolaris in Rat Livers 45
O - Latent Infections and the Pathogensis of Rat Virus (RV) Infections in Hamsters and Multimammate Rats 46
P - The Potentiating Effect of Latent Trichinosis in Rats on Infection and Disease Due to EMC-Virus 47
Q - Adaptation of Rat Virus (RV) and K Virus to Suckling Virus 48

R - Thermo-reproduction in Relation to Virulence of Viruses 49
S - Processes of Cell Infection by Virus as Investigated by Transformation Process and Viral DBAS 50
T - Studies on Antimicrobial Activity of Abalone Juice 51
U - Influenza Viruses 52
V - Adenoviruses 53
W - Vaccines for Multiple Respiratory Viruses 54
X - Pneumococci 55
Y - Tumor Viruses 56

Laboratory of Biophysics and Biochemistry

A - Studies of the Inactivation of Viruses 57
B - Physical and Chemical Characterization of Viruses 58
C - Development of Methods for the Chemical Analysis of Biological Products 59
D - Effect of Sunlight on the Molluscicidal Activity of Sodium Pentachlorophenate 60
E - Properties of the Sera of Guinea Pigs Inoculated with Diphtheria Toxoid and Freund's Adjuvant 61

Laboratory of Blood & Blood Products

A - Development and Application of Control Procedures for Blood and Blood Products 62
B - Stability and Potency of Blood Fractions 63
C - Development and Application of Immunohematological Research Procedures 64
D - Stability and Potency of Formed Blood Elements 65

The accelerated pace of research during the past ten years in the area of infectious diseases has resulted in a significant increase in the number, complexity, and diversity of biological products. At the close of the calendar year, 279 such products were licensed under the provisions of the Public Health Service Act for commercial use in this country and abroad.

These products, which include the vaccines, antitoxins, therapeutic serums, and human blood and its derivatives, are developed for the most part from pathogenic or potentially pathogenic microorganisms. Their preparation requires careful control in order to minimize safety hazards which might occur in the course of processing, and to ensure final products of satisfactory potency. Accuracy is essential in every step, for the end product is the preservation of human life.

Responsibility for the administration of these control measures resides with the Division of Biologics Standards. Effective administration of these responsibilities requires the design and development, within a research context, of adequate and practical standards for the production and testing of biologics, careful surveillance of production methods, and the continuous improvement of testing procedures. Thus the control program of the DBS is necessarily supported by an active and flexible research program, enabling the Division to keep pace with the rapid development of new and improved immunizing agents and to prepare physical references as well as to develop testing procedures for these products once they are ready for commercial production. The essential features and philosophy of this program were discussed in last year's report and need not be repeated.

In addition to providing information as it is needed to meet the problems encountered in this increasingly complex field, the DBS research program also provides a reservoir of trained scientists whose services are available when such problems arise.

Currently staffed with 62 principal investigators and approximately 106 supporting personnel, excluding administrative staff, the Division's research programs include a diversity of projects--many of immediate practical urgency, and having direct relation to the prime responsibilities of the Division. Others may be regarded as having a stake in the future, since demands in this area are likely to arise suddenly and move with unpredictable speed. Although the basic objectives of the Division are clearly known and the areas of research are self-evident from the nature of the mission of the Division, most of our scientists--except those with continuing and full-time administrative responsibilities--are encouraged to devote up to one-half of their time to research projects of their own devising. Many worthwhile leads have developed from such investigations, and many more can be expected to emerge in the future; the basis for this policy, however, is the need for a reservoir of trained and program-oriented scientists.

While the main activities of the Division are covered in some detail elsewhere in this report, a few items of special interest should be mentioned here.

Activities during the past year have been dominated by the problems presented by poliomyelitis vaccine--both the inactivated and live attenuated.

A great deal of effort was concerned with matters leading to the eventual licensing of live poliomyelitis vaccine. Numerous conferences were attended by staff members and a number of meetings of the Public Health Service Committee on Live Poliovirus Vaccine were held. The entire situation is perhaps best summarized in the series of papers, presented at the American Medical Association clinical session held in Washington November 30, 1960, and published in the March 11, 1961 issue of the Journal of the American Medical Association.

The main problem as far as the Division is concerned has been the development of standards--both physical standards, (standard preparations to be used by laboratories engaged in standardization work) and written standards (regulations setting forth the requirements which must be met with respect to safety, purity and potency).

Development of the written standards has been a complex and difficult task, conducted, perforce, in an atmosphere of intense public interest and in the face of a variety of freely expressed and sometimes irreconcilable points of view. The preliminary step was the issuance of a report by the PHS Committee on Live Poliovirus Vaccine on August 24th, which outlined the principles. This was followed on August 25th by a set of specifications applicable to the testing of live poliovirus vaccine. After frequent discussions and consultations with those concerned, including the scientists involved as well as prospective manufacturers, a Notice of Proposed Rule Making--the necessary preliminary to the formal adoption of Regulations--was published in the Federal Register on November 23, 1960. It had originally been visualized that the manufacturing development would proceed simultaneously with the development of Regulations, so that the live poliovirus vaccine might become available as a licensed product at about the time that Regulations were formally adopted. It does not now appear that this will be so, nor does it appear that any appreciable quantity of vaccine will become available until late in 1961.

A problem of another type was presented by the publication of an article by the Massachusetts Department of Public Health that, in their experience, the pertussis component of the diphtheria, tetanus, pertussis, and poliomyelitis multiple antigen was unstable. This has given rise to a lengthy and difficult program of examining the stability of the pertussis component of a variety of such preparations. This work was under way at the end of the year and a report will be made early in 1961.

The favorable situation with respect to the rise in the potency of inactivated poliomyelitis vaccine (Salk vaccine) reported last year continues and the average potency of the vaccine in 1960 reached unpredicted levels.

In November, investigators from university, pharmaceutical, and NIH laboratories were invited by DBS to present their findings in the development of a satisfactory immunizing agent against measles in order to assess and correlate the progress made since their last meeting in 1958.

Dr. John Enders, whose work with measles virus established the principles for an attenuated measles vaccine, summarized his recent experience with the Edmonston strain of virus grown in chick embryo cells. Clinical data presented by other groups, using live vaccine made from this strain, gave evidence of its capacity to elicit satisfactory protection against natural measles as well as specific antibodies among the vaccinees.

Measles vaccine was shown by three groups of investigators to protect children exposed to natural virulent measles virus against the illness, while the unvaccinated controls showed the expected high incidence of the disease. Evidence of satisfactory antibody titer at the end of 18 months was also presented. Close to 1,000 children have been given this vaccine.

Live measles vaccine, in most cases, caused some clinical reactions--principally fever. However, Dr. Frederick McCrumb, of the University of Maryland, presented information indicating that concurrent administration of live vaccine and gamma globulin markedly suppressed the expected febrile reaction without interfering with the development of antibodies. In addition, Dr. F. A. Gibbs, of the University of Illinois School of Medicine, presented electroencephalographic findings showing that children given live measles vaccine showed little or none of the EEG abnormalities seen in children with naturally acquired measles.

Although various methods of preparing the vaccine have been used, propagation in chick embryo tissue culture is preferred since adventitious agents which might be pathogenic for man are less likely to be encountered.

There has been some question in the past whether a live vaccine of sufficiently high titer could be produced which would maintain its potency during storage. It is now generally agreed that this problem has been solved and that vaccine of high titer can be consistently produced and maintained in stable form in the dry state.

The DBS has developed serologic tests for the detection of measles antibodies, and data pertaining to standardization of the complement fixation and neutralization tests was presented. A dried reference serum has been prepared and its place as a control in development studies and vaccine production was discussed.

As a result of the conference, an increasing volume of work can be expected from the various investigative groups in acquiring larger clinical experience. The DBS plans to continue to coordinate and expedite these studies since, for the first time, there is a general feeling that vaccination of man against measles is an attainable, practical goal within the immediate future.

The exchange of ideas and technical knowledge with other laboratories working in related areas has proved of great value to the Division's research programs. Dr. Gerald L. Van Hoosier, of the Laboratory of Virology and Immunology, returned to DBS in August after a year's study under Dr. Edwin H. Lennette, chief of the Viral and Rickettsial Disease Laboratory, California Department of Public Health. While there, Dr. Van Hoosier worked with a variety of disease agents. His principal projects were the fluorescence microscopy of the enteroviruses, and the chemistry of influenza.

Dr. Samuel Baron, also of LVI, left DBS in June for a year's study in London at the National Institute for Medical Research, in the laboratory of Dr. C. H. Andrews, well known authority on respiratory diseases. While there, he will continue his work in the immunology of viral diseases.

Dr. Frank Perkins, of the British Biological Standards Control Laboratory, returned to Hampstead, England, in July after a year's work with the Division. A member of the British Medical Research Council staff since 1955, Dr. Perkins has conducted laboratory studies connected with clinical trials of polio-myelitis vaccine in England, and his year in the DBS viral research laboratories was mutually profitable.

Dr. Mitsuo Yokoyama, chief consultant of the Blood Typing Laboratory and the Rh Center of the Tokyo Medical and Dental University, has been with the DBS Laboratory of Blood and Blood Products for more than a year. An authority on blood grouping and its application to various populations, Dr. Yokoyama is currently studying antibodies to rare human blood group factors in animals by immuno-electrophoresis.

As in past years, there has been a constant flow of visitors through DBS laboratories from foreign countries during the past 12 months. Among these have been scientists from England, Australia, Germany, Russia, Japan, France, and Canada. Others came from Thailand, Finland, South Africa, India, Pakistan, Czechoslovakia, Hungary, Yugoslavia, Venezuela, Chile, and Colombia. Many were interested in the DBS studies relating to poliomyelitis vaccines; some in biologics control procedures in general, some in blood banking. Arrangements to meet the needs for the exchange of scientific information with these visitors is a time-consuming but necessary part of the activities of the Division since many of these visitors are concerned with biological control activities in their own countries.

The Board of Scientific Counselors, which is primarily concerned with the research program of the Division, met with the Director's staff and laboratory chiefs in December. The meeting was essentially one of orientation for the Board's new members, Dr. Benjamin Alexander of Harvard University, and Dr. Scott Neil Swisher of the University of Rochester. They replace Drs. David Bodian, Johns Hopkins University School of Medicine, and Robert Pennell, Protein Foundation Laboratories. Both of the new members appointed for four-year terms, are well known in the field of hematology. Dr. Alexander is associate professor at Harvard Medical School and associate director of the Beth Israel Hospital in Boston. His special areas of research are blood

coagulation, and hemorrhagic diseases, with special reference to the biochemistry of prothrombin. Dr. Swisher is associate professor and chief of the Division of Hematology at the University of Rochester School of Medicine. His special interests are human hemolytic disorders and he is also active in blood banking.

The Board expressed satisfaction with the scope of the DBS research programs and the general capabilities of the research staff, as well as the marked improvement in laboratory facilities. The suggestion was made that the addition of a biometrician to the staff, to promote and extend the use of mathematical and statistical methods and to assist in the design and evaluation of biological research, would be of value to the Division.

The major event for DBS this year was the long-anticipated completion of the Division's new quarters, which have been under construction since the spring of 1958. Formal dedication ceremonies took place on June 30, 1960.

His Majesty Bhumibol Adulyadej, King of Thailand, officially dedicated the new DBS building with the unveiling of an inscribed bronze plaque, to be placed in the main entrance*.

The invitation to participate in the ceremonies was extended to King Bhumibol because of his active role in health measures in his own country and because of the long association of his family with medical science. Additional interest developed following the return of the U. S. Cholera Research Advisory group, headed by Dr. Joseph Smadel, which visited the SEATO and other Asian countries in 1959 and was granted an audience by King Bhumibol in Bangkok at that time.

The dedication ceremony itself demanded extraordinary organizing effort on the part of those directly concerned, particularly Dr. Tomlinson, Assistant Director, Mrs. Butterly, Information Officer, and Mrs. Lynch of my immediate staff.

Occupancy of the new building was initiated in September 1960, and completed in January 1961. Although beset with all the inherent difficulties of moving and resettling laboratories which had been housed in four separate buildings, and the consequent dislocation, the advantage of having all operations under one roof should soon have a favorable influence on our programs. Good progress has been made in improving coordination of various projects previously scattered, although some programs are still delayed due to the lag in completion of specific building alterations. Because of increased program demands, space--particularly in the animal areas--is more

---

* "Science and Peace will triumph over ignorance and war, nations will unite, not to destroy, but to build, and the future will belong to those who will have done most for suffering humanity."

. . . Louis Pasteur

limited than had been anticipated when the building was originally designed; in fact, as we re-evaluate our needs we come to the conclusion that additional space will be necessary to meet the continuing and expanding responsibilities of the Division.

Occupancy of the new building has made it possible to reorganize the functions of the Division in the field of virology--a step which had been visualized for some time but had not been possible, due mainly to poor space arrangements. The Division's program in virology was strengthened by the addition of Dr. Joseph E. Smadel who joined the DBS staff on August 7, 1960.

The reorganization involved the establishment of three new laboratories, replacing the former Laboratory of Viral Products: the Laboratory of Viral Immunology, headed by Dr. George Hottle; the Laboratory of Virology and Rickettsiology, with Dr. Smadel as chief; and the Laboratory of Biophysics and Biochemistry, headed by Dr. Caspar W. Hiatt.

The Division now consists of six laboratories. The more important activities of these laboratories are summarized as follows.

LABORATORY OF CONTROL ACTIVITIES (Dr. William G. Workman, Chief)

The Laboratory of Control Activities, supported by sections on control tests, pyrogens, and reference standards, is responsible for activities dealing directly with licensed establishments in relation to the licensing and control of biological products.

Its activities include:

(1) Determination of eligibility of establishments and of individual biological products for license. This determination is made on the basis of the integrity of management and technical personnel, the physical facilities for manufacturing and testing of products, scientific and professional qualifications of personnel and, the evidence of continued safety, purity, and potency of products for which an application for license is being evaluated. License applications are usually reviewed by committees or groups consisting of appropriate staff members.

(2) Supervision of annual and special inspections of licensed establishments and of those for which an application for license has been made.

(3) Release of individual lots of biological products for distribution by manufacturers on the basis of manufacturer's review, DBS tests, and other information relating to the safety, purity and potency of that particular lot of the product.

(4) The establishment and distribution of physical biological standards, reference preparations, and control materials. A small culture collection is also maintained, mainly for use by the Division and licensed manufacturers.

(5) Review of requirements and regulations now in effect for such constructive revision as is needed, and for the development of requirements and regulations for new products.

(6) Maintenance of close working relations with other laboratories of the Division and other agencies to insure continuous knowledge of information needed for the licensing of establishments and new products and for the testing and release of individual lots of licensed products.

During the twelve month period, December 1, 1959--November 30, 1960, a total of 7,206 control tests were carried out to insure the sterility, safety, potency, and purity of licensed biological products. These included: routine products for release, 5,984; inspection samples, 1,193; and complaint investigations, 29. The results of these tests served as a basis for the release or rejection of individual lots or products. In addition, 1,386 cooperative service tests were done on biological products not licensed.

During the same period, 4,894 lots of biological products were submitted for release by licensed manufacturers. Of these, 4,848 lots were released, 12 lots rejected, and 34 lots withdrawn from consideration for release by manufacturers.

To maintain an adequate supply of physical reference standards for use by the licensed manufacturers in their official control testing, it is necessary to prepare and standardize new liquid lots from the primary dried stocks. The number of lots prepared and standardized during the year were: antitoxins, 12; serums, 2; vaccines, 5; toxoids, 6. A total of 112 tests were required to complete a satisfactory standardization of these lots. These tests include flocculation reactions, animal protection tests, animal potency tests, neutralization tests, and a number of specialized tests for specific products.

Standards, reference preparations, and cultures are freeze-dried for greater stability during storage. The following were dried between January 1, 1960, and December 9, 1960.

	Ampules
Cultures	2200
Serums	675
Vaccines	1015
Viruses	717
Toxins	274

Official standards, reference, and control preparations currently maintained include 64 items.

Standards, reference preparations, and cultures were distributed to research or control laboratories of licensed manufacturers, health departments, or universities in this country and abroad as follows:

Antitoxins	337
Serums	1635
Vaccines	1655

//

Toxins..... 126
Cultures..... 462
Viruses..... 268

LABORATORY OF VIRAL IMMUNOLOGY (Dr. George A. Hottle, Chief)

Some of the responsibilities of the former Laboratory of Viral Products were assumed by the Laboratory of Viral Immunology at the time of its formation in July, 1960. These responsibilities include both research and control activities.

Work with vaccines to prevent poliomyelitis constituted the main activity of the Laboratory. The properties of the polioviruses which have been used in the preparation of the oral, attenuated poliovirus vaccine have been investigated, and steps have been taken to acquire a supply of the viruses for use as reference preparations. The revelation that vaccines prepared in Macaca kidney cell cultures contained a contaminating agent (the vacuolating virus) has stimulated an examination of vaccine preparations in cell cultures prepared from African green monkeys, in which the virus can be readily detected. Studies on neurovirulence of the vaccine viruses for monkeys have continued; the results were reported at the Second International Conference on Live Poliovirus Vaccines held in Washington in June, 1960.

The control of the killed virus poliomyelitis vaccine continues to be an important part of the program. The decline in incidence of poliomyelitis in 1960 has been accompanied by a decrease in demand for the vaccine. With the stocks of vaccine remaining in the manufacturers' cold storage, production of the vaccine has been greatly curtailed. One manufacturer, Merk Sharp & Dohme, has developed a purified vaccine which was marketed for the first time during the summer.

During the year, the following tests were carried out on killed poliomyelitis vaccine:

Tissue culture safety tests.....54
Monkey safety tests.....32
Potency tests in monkeys.....45
Potency tests in chicks.....101

The Laboratory participated in a joint study of potency of poliomyelitis vaccine sponsored by the World Health Organization. The purpose of the study was to correlate the results of potency tests in monkeys and chicks and in tissue culture by the neutralizing antibody combining test. Among the vaccines included in the study was the current DBS reference vaccine.

The relative merits of potency tests in monkeys and chicks continue to be studied. It is planned that an evaluation of the chick test in relation to the monkey test will be possible when the results of the WHO study are made available.

Although the potency of poliomyelitis vaccine has continued to increase

during the year, occasional problems with individual lots continue to appear. A proposal to raise the minimum acceptable level by 50 percent was made late this year in order to eliminate vaccines which show low potency.

During the year, the following tests were carried out on adenovirus vaccine:

Tissue culture safety tests...14

Monkey safety tests..... 8

A strengthened interest in adenovirus vaccine developed during the year. One new license was issued to Pitman-Moore Laboratories, bringing the total number of licensed manufacturers to three. Recently, other establishments have expressed an interest in this vaccine. An emerging problem concerns the continued potency and immunogenicity of the products available.

Comparison of the neurovirulence for monkeys of the strains of attenuated polioviruses after intramuscular inoculation has been made. It was found that the Lederle Type I strain has the ability to cause paralysis in monkeys after inoculation of at least $10^{7.7}$ PFU of virus. While the other strains all have the capacity to produce histologic lesions of poliomyelitis they do not cause paralysis. These results were also reported at the Second Conference on Live Poliovirus Vaccines, and have been stressed in the reports of the PHS Committee on Live Poliovirus Vaccines.

Studies on reversion of attenuated polioviruses to increased neurovirulence for monkeys after passage through the human alimentary tract indicate that this can occur. Furthermore, it has been found that passage of virus in either a liquid tissue culture system or in a plaque system causes changes in the virus. It was concluded that all studies characterizing the excreted virus must be done directly on fecal material.

By means of the immuno-inactivation method for detecting virus antibody in serum, it was possible to find extremely low levels of antibody to enteroviruses in the sera of persons with hypogammaglobulinemia.

Delayed hypersensitivity in guinea pigs has been established to vaccinia virus following inoculation of live or dead virus; the normal cycle of infection and recovery was observed despite the inhibition of antibody mechanisms by use of radiation and antimetabolites.

LABORATORY OF VIROLOGY AND RICKETTSIOLOGY (Dr. Joseph E. Smadel, Chief)

The Laboratory of Virology and Rickettsiology was established in the summer of 1960, bringing together a number of groups of DBS workers and one group formerly in NIAID.

The objectives of the Laboratory are to improve the materials and procedures now available for immunizing man against a number of viral and rickettsial diseases, e.g., influenza and typhus, and to develop the necessary immunologic tools for use against certain of the diseases which are not as yet adequately controlled by immunoprophylaxis, e.g., measles. In order to attain such objectives, the efforts of the staff range widely from basic biological and virological research to classical immunological work on the preparation and assay of potent antigens and on their evaluation in man.

One of the most active fields of interest encompasses two new live attenuated viral vaccines--poliomyelitis vaccine and measles vaccine. The principal problem encountered with live attenuated polio vaccine--one which has engaged the attention of members of this Laboratory as well as others in DBS and in industry--centers around methods for producing the live vaccine free of extraneous agents, particularly the ubiquitous foamy virus and vacuolating virus which contaminate many of the monkey kidney tissue cultures used for growing polio viruses. Part of the effort, which is in the hands of Dr. Harry Meyer and his group, is concerned with improving and developing serological methods for determining whether vacuolating virus infection is or is not present in monkeys prior to the time their kidneys are used for the preparation of tissue cultures.

Dr. Anthony Morris and his group, in collaboration with investigators of NIAID, have studied the pathogenicity of vacuolating virus in man. In brief, when given by the respiratory routes in appreciable amounts, vacuolating virus causes no obvious disease but elicits specific antibody production and can be recovered from the upper respiratory tract a week or so after inoculation. The work of others had already indicated that similar amounts of virus when fed by mouth failed to multiply in man.

Another approach made by Mrs. Hope Hopps has concentrated on the development of continuous cell lines from several simian hosts, with the objective of obtaining a tissue culture procedure for detecting and maintaining vacuolating virus unhampered by the presence of this agent as a contaminant in primary monkey cell cultures. This approach has not yet been successful, but the results have been sufficiently encouraging to continue the venture.

Many of the pressing problems associated with the development of measles vaccine are similar to those mentioned above which plague the live poliovirus vaccine program. One of the most important of these is the frequent infection of monkeys with measles virus by the time they reach the Laboratory. Although monkey cell cultures are not used for the growth of attenuated measles virus (chick embryo tissue cultures are employed), susceptible monkeys are essential for the experimental work on the immunogenicity and pathogenicity of attenuated strains and will be necessary in the future for certain types of assay procedures which will be applied to each commercial lot of vaccine.

Serological methods for selecting susceptible monkeys and procedures for bringing the nonimmune monkeys from their natural habitat to the investigator without intercurrent infection are being examined. During the year, a collaborative effort was initiated between this Laboratory and the

Department of Pediatrics at Walter Reed Army Medical Center which should provide DBS with a clinical testing outlet for its investigations on live measles vaccine.

Dr. Morris's Section has as its primary mission the development and improvement of methods for immunizing man against the rickettsial diseases, particularly typhus and Q fever. Although the subject is not new, and reasonably good vaccines are available, there are cogent reasons for continuing to press on.

In typhus immunization, there is great need for 1) stable preparations which can be stockpiled by highly developed countries for use in a limited emergency, and 2) a live attenuated vaccine which can be produced in the event of a catastrophe, even in underdeveloped areas. Progress along both of these lines is satisfactory. A killed purified dried Rickettsia prowazeki preparation is being studied on a continuing but limited basis in the Laboratory and on a collaborative basis at the University of Maryland School of Medicine in volunteers. Methods for producing, assaying, and stabilizing the E strain of R. prowazeki (originally employed by Gallardo in the early 1940's and extensively studied subsequently by Fox) are being developed.

The disease, Q fever, is spreading rapidly in the bovine population of the United States, and increased numbers of human cases are to be anticipated. Although a potent experimental Q vaccine is available, there has been little general demand for its use outside the military services, and no licensed commercial Q vaccine is being produced. Efforts are being made to develop a set of recommendations which would provide an essential step in the eventual licensing and commercial production of Q vaccine. In addition, experiments are under way to study the feasibility of a combined Q and typhus vaccine.

Viral hepatitis is a matter of interest to several groups in DBS. The contamination of blood products by the virus associated with homologous serum jaundice constitutes one of the serious problems in medicine. Moreover, continuing efforts to transmit the agent of viral hepatitis in systems other than volunteers have given discouraging results in this Division and in many laboratories throughout the world. Despite these negative results, occasional flurries of enthusiasm have swept the field, lasting until it became apparent that each newly discovered "hepatitis virus" was unrelated to the disease in man. Despite this background of frustration and occasional wishful thinking, the recent work of Dr. Joseph O'Malley on an agent which may have some relation to viral hepatitis in man again raises a hope. This virus, recovered in tissue culture from the NIH-6 icterogenic human plasma pool, which had been used some years ago in volunteer studies, is associated with what appears to be a specific serological response in human beings. Serum specimens from some of the former volunteers in viral hepatitis studies are without antibodies prior to infection, but contain antibodies against the new agent during convalescence. Because of the potential importance of the work, investigation of this new agent is being pursued.

At the present time, the only continuing responsibility for the routine assay of commercially produced vaccines in this Laboratory is connected with

the influenza and adenovirus vaccines. The currently available assay procedures in both instances leave much to be desired, but productive experimental investigations which might solve some of the problems have been limited. Efforts along these lines will be intensified during the coming year.

A number of the current investigations of the Laboratory bear little direct relationship to the primary mission. Nevertheless, some of these indirectly support the responsibilities of the DBS, and others are interesting and productive. Among these are the studies of Dr. Lawrence Kilham on rat virus, and those of Dr. Bernice Eddy on polyoma virus and what appears to be a hitherto undescribed tumor in hamsters. The work of Dr. C. P. Li's group on the antibacterial and antiviral properties of abalone juice calls attention to an entirely new source of antibiotic substances.

LABORATORY OF BACTERIAL PRODUCTS (Dr. Margaret Pittman, Chief)

The work of the Laboratory of Bacterial Products is devoted to research and regulatory activities. During the year, several changes in organization and staff were made. The Section on Cancer Products was transferred to the Laboratory of Virology and Rickettsiology, and the name of the Section on Haemophilus Studies was changed to Section on Bacterial Vaccines. The Section on Bacterial Toxins continued to operate with a deficiency of staff members. Two new staff members--Dr. Harold Baer and Dr. Sotiros D. Chaparas--commenced work in the Section on Allergenic Products. Dr. Lajos Csizmas, Visiting Scientist for 3.75 years, resigned on October 1.

Studies relating to pertussis products, cholera vaccine, Schick test toxin, and PPLO contamination of tissue cultures were continued. New studies on typhoid vaccine, tuberculin, and blood group substances were initiated. Studies on immunological responses to multiple antigen vaccines and sterility test media for fungi were discontinued due to staff resignations; it is hoped that they can be activated in the near future.

Due to the day-to-day problems which have arisen in regard to toxicity and potency of pertussis vaccine, the Laboratory has continued to carry out the control testing of this product. Constant surveillance is maintained and investigations are carried out to find the cause of undue mouse toxicity and other undesirable changes. A special investigation was undertaken in connection with a complaint of instability of potency of pertussis vaccine in quadruple antigen vaccines.

The following tests relating to regulatory actions were performed:

Potency Tests	
Pertussis vaccine (lots for release inspection, complaint)	219
Anti-*haemophilus influenzae* Type b serum	5
Haemophilus influenzae typing serum	7

Freedom-from-toxicity tests	
Pertussis vaccine	244

In the cholera vaccine study, the main problem remaining before the use of the newly developed quantitative mouse protection test for potency evaluation can be recommended is the preparation of dried reference vaccines. Unlike the results obtained in the drying of other bacterial vaccines, a marked drop--as much as tenfold--was obtained with cholera vaccine. Study of this problem will be pursued. In coordinating this study with the SEATO Cholera Research Program, bacteriological equipment was selected for shipment from NIH. Dr. John Feeley of this Laboratory, organized the equipment in the newly established Pakistan-SEATO Cholera Research Laboratory in Dacca; he also participated, while in Dacca, in the first Conference on Cholera under the auspices of the SEATO Program. A large number of cholera cultures from Thailand have been received, examined, dried, and distributed to participating cholera research scientists.

The diphtheria toxin to be designated as the U. S. reference for the Schick test toxin was dried commercially. Studies are now in progress (1) to determine stability during the process of drying and during storage at high temperatures, and (2) to relate its activity to that of the international reference preparation. Based on the results of the total study, a proposed revision of the requirements for this product will be prepared.

In the studies on pleuropneumonia-like organisms in tissue cultures, it was demonstrated that fluorescent antibodies against a tissue culture PPLO strain reacted specifically with PPLO-contaminated tissue cultures but not with PPLO strains from other sources or with 24 different bacterial species.

Participation in the laboratory phase of a World Health Organization project on the evaluation of typhoid vaccine has been initiated. This Laboratory is one of a number of international laboratories participating in the laboratory evaluations of two specially prepared lots for use in clinical field trials in three countries. It is hoped that out of the various tests employed, one will provide results which will show a correlation with protective activity in man and ~~that~~ can be recommended eventually as the standard laboratory test for potency evaluation of typhoid vaccine.

In the newly activated Section on Allergenic Products, a study was initiated on an analysis of the antigen complexes of various mycobacteria in order to obtain basic information applicable to improvement in the specificity of tuberculins. In cooperation with LBBP, specific blood groups were found to be present in urines.

The Laboratory is serving as a depot and distribution center of ragweed pollen for the Committee on Standardization of Allergens, which is functioning within the extramural activities of NIAID. This and other liaison activities provide helpful connections relating to the development of regulatory standards for allergenic products.

Regulatory activities, in addition to the control testing of pertussis vaccine and Haemophilus influenzae products, have consisted of reviews of license applications for bacterial products in single and multiple antigen vaccines and of revisions in manufacturing procedures, participation in yearly

inspection of establishments, and in the formulation of additional standards or revision of standards for bacterial and allergenic products for inclusion in U. S. PHS Regulations for Biological Products.

LABORATORY OF BLOOD AND BLOOD PRODUCTS (Dr. John T. Tripp, Chief)

The research program of the Laboratory of Blood and Blood Products has as its goal the improvement of testing procedures used for the control of biologic products derived from blood. The investigations cover all phases of blood collection, processing, shipment, and storage. The research interest encompasses not only improvements for existing control procedures but also is directed toward new tests for control of new products.

Many of the products under development have immunological or biological activities for which there are no established test criteria. This uniqueness often requires that research on fundamental properties be carried out before definitive control tests can be devised. A good example is the investigation of components of the coagulation system that was started two years ago in anticipation of introduction of such products on the market. Information gained from these studies has been applied in standards for fibrinolysin (human).

Other research interests of importance to the control program include:

Studies of blood containers, particularly those of plastic, to determine possible effects of such materials on the blood. Investigations of several aspects of immunological reactions of blood group antigens and antibodies to enable more significant standards to be established.

Determination of changes that occur during processing and storage of blood and blood products. This is a continuing fundamental study designed to yield information leading to better standards for purity, potency, and expiration date.

Studies of the use of platelets in leukemia. As part of this work, the effects on donors of repeated large platelet donations by plasmapheresis are being investigated to establish dating period and needs for specific control procedures.

An "extramural" program of the Laboratory derives principally from its obligations to other organizations. Many of these obligations stem from the legal requirements of the control functions of the Laboratory, others from a need to utilize all available sources of information in establishing standards for blood and blood products. As the number of establishments engaged in collecting and processing blood--now more than 400--increases, the need for a centralized organization to help coordinate such matters as technician training, reference serums, and consistent technical information becomes more apparent. Within the limitations of time and staff, the Laboratory has assisted in each of these areas. Arrangements have been formalized for the expeditious handling of requests to store or to supply blood or rare and unusual types. Using a

technique developed in this Laboratory, such blood is stored at extremely low temperatures, allowing preservation for long periods of time. The Laboratory is now engaged in the preliminary aspects of a study of the interchangeability of American equipment for taking, storing, and giving blood. This work is being done on a cooperative basis with the American Standards Association and the International Standards Organization.

Serial No. DBS 1
1. Office of the Director
2. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Program direction and administration for the Division of Biologics Standards is centered in the Office of the Director, with centralization of administrative procedures relating to personnel, travel, supply and accounting. Major objectives are determined and program responsibilities are assigned to the operating units within the Division. For each major area, staffing patterns are developed and are continually reevaluated in relation to program changes. The required financial support is determined for each area in relation to the Division's total budget. A major activity of the Office of the Director is the maintenance of the proper balance between the control activities and the research programs, the latter being supported to the degree that such investigations are required in order to meet the control responsibilities of the Division.

The Director working with members of his immediate staff, including a legal assistant, conducts a continuing review of existing regulations for the control of biological products, making revisions as necessary and also develops additional regulations as required for new products.

Close and continuous liaison is maintained with technical representatives of industry. Frequent meetings are held between members of the Division's professional and administrative staff and groups of manufacturers who are concerned with common problems. In addition, 150 to 200 conferences are held each year with technical representatives of manufacturers who desire to discuss production and testing programs peculiar to their own organization.

The production of poliomyelitis vaccine continues to be closely monitored through the operation of the Technical Aid Program. A liaison scientist, under the direct supervision of the Director, is assigned to each of the establishment manufacturing this product. These individuals routinely visit the industrial plants and maintain close liaison with the technical and research staffs of the producers.

The Office of the Director services the Technical Committee on Poliomyelitis Vaccine, the Public Health Service Committee on Live Attenuated Poliomyelitis Vaccine, as well as numerous Ad Hoc Committees which are appointed from time to time to consider matters relating to the control of biological products.

During 1960 a considerable amount of time was devoted to problems related to live poliovirus vaccine. The immediate problem for the Division was the development of standards for live poliovirus vaccine -- looking toward the possibility of licensing of this product in the coming months.

This has been an extremely difficult and time consuming process involving many meetings with the Committee on Live Poliovirus Vaccine as well as a number of meetings with international groups.*

The Director, or his designated representatives, attends meetings of committees and advisory groups of the World Health Organization, as well as those of the National Research Council, Armed Forces Epidemiological Board, etc. During 1960, Division scientists have taken an active part in the World Health Organization's program for the development of international uniformity of biological products.

Within the Office of the Director, the Information Office continues to be concerned with, (1) communications through such media as press, radio, television, publications and exhibits of information to the public on the Division's control and research activities, and (2) internal communication of such information through reports to the Director, NIH, and to the Surgeon General as well as to the Department and to the Congress.

During 1960, a great deal of time and attention was devoted to the problem of moving into the new building and in making these facilities fully functional. This move was accompanied by a reorganization of the virus activities. The rather large Laboratory of Viral Products was separated into the following 3 laboratories:

Laboratory of Viral Immunology
Laboratory of Virology and Rickettsiology
Laboratory of Biochemistry and Biophysics

Serial No. DBS 2
1. Control Activities
2. Office of the Chief
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Office of Chief, Laboratory of Control Activities

Principal Investigator: Dr. W. G. Workman

Other Investigators: None

Cooperating Units: Three

Man Years:
Total: 3
Professional: 1
Other: 2

Patient Days: None

Project Description:

Under the Director, Division of Biologics Standards, this project is responsible for activities dealing directly with licensed establishments in relation to establishment and product licenses and the control of biological products. These activities are supported by sections on reference standards, on control tests, and on pyrogens.

The activities include:

(a) Determination of eligibility of establishments and of individual biological products for license. This determination is made on the basis of a review of the integrity of management, of the physical facilities for manufacture and testing of products, of the scientific and professional qualifications of personnel, and of the evidence of continued safety, purity, and potency of products for which an application for license is being evaluated. Recommendations for establishment and product licenses are usually made by an ad hoc committee consisting of appropriate members of the staff of the Division.

(b) Supervision of annual and special inspections of licensed manufacturers and of establishments for which an application for license has been made.

(c) Releasing of individual lots of biological products for distribution by manufacturers on the basis of review of manufacturer's and DBS tests, and of other data relating to the safety, purity or potency of the individual lot of the product.

(d) The establishment and distribution of physical biological standards, reference preparations and control materials. A small culture collection is also maintained mainly for the Division and licensed manufacturers.

(e) Review of requirements and Regulations now in effect for such constructive revision as is needed and development of requirements and Regulations needed for new products.

(f) Maintenance of close working relations between this Laboratory and the other Laboratories of the Division in order to insure continuous knowledge of all activities and information needed for licensing of establishments and of new products and for the testing and release of individual lots of products currently licensed.

(g) Serving on various committees and collaborating with other official or non-official agencies concerned with the manufacture, testing or control of biological products.

(h) Cooperation with other government agencies particularly the Department of Defense for interchange of information relating to the control of biological products and their use in preventive medicine.

(i) Maintains contacts with other workers in preventive medicine in this country and abroad.

Significance to Division of Biologics Standards: This project is directly related to the legal responsibilities and administrative functions of the Division, and requires close liaison with the research activities of the Division in order to put new knowledge to practical use.

Proposed Course of Project: It is proposed to continue the activities of this Laboratory at essentially the present level but with increased emphasis on the establishment and use of reference standards and on improvements in control testing procedures.

Serial No. DBS 3
1. Control Activities
2. Control Tests
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Control Testing and Investigations Related to Control of Biological Products.

Principal Investigator: Mr. Robert W. Kolb

Other Investigators: Mrs. Claire B. Cox
Mr. Otis L. Green
Mr. Harry T. Aylor

Cooperating Units: Colonel Abram S. Benenson, Mc., USA
Director, Division of Immunology
Walter Reed Army Institute of Research
Walter Reed Medical Center

Man Years:
Total: 12
Professional: 3
Other: 9

Project Description:

The principal objective of this project is to assure the compliance of licensed biological products with standards established under the biologics control provisions of the Public Health Service Act. Individual lots of biological products are recommended for release on the basis of evaluation of the manufacturer's and Division of Biologics Standards tests. The evaluation includes control testing for sterility, safety, potency and purity as required for licensed biological products including antitoxins, therapeutic immune serums, blood and blood derivatives, bacterial vaccines, toxins and toxoids, multiple antigens, viral and rickettsial vaccines, diagnostic substances for dermal tests, antivenins, venoms and allergenic extracts. Supplemental to control testing are the following activities: (a) Evaluations of manufacturers' protocols of tests on lots of biological products for compliance with minimum standards; (b) preparation of releases; (c) maintenance of a permanent record and filing system for releases, protocols of manufacturers' tests, and samples of all biological products submitted to the Division and (d) a continuing reevaluation of methods and operations relative to the establishment of efficient control measures.

In addition to the above activities are a number of research and other functions which have been related to this program as follows: (a) Research dealing with the development of new methods for the control of biological products and designed to improve existing in vivo and in vitro methods of testing; (b) research concerned with the study of stability of biological products and with the development and standardization of new biological preparations; (c) participation in the establishment and product licensing program, which involves the review and screening of new license applications, testing of products submitted in support of such applications, prelicensing inspections and preparation of official reports; (d) participation in the annual inspection program of licensed biological establishments and the control testing of inspection samples collected; (e) participation in the revision and formulation of regulations and additional standards for biological products; (f) cooperative investigations with intra-agency laboratories, commercial establishments, domestic and foreign governmental agencies in which studies and assays are carried out on numerous biological and pharmaceutical preparations; and (g) the orientation and training of new government personnel and visitors from other domestic and foreign health laboratories and institutions in biological control testing methods and related operations as conducted within the Division.

Major Findings and Accomplishments:

I. Control Testing Activities

(a) During the past 12 months (i.e December, 1959 through November, 1960) biological products manufactured under U. S. Government license have been tested for conformance to Public Health Service standards, regulations, and requirements. A total of 7,206 control tests were carried out in the Laboratory of Control Activities to insure the sterility, safety, potency and purity of biological licensed products. These are summarized as follows:

Routine Products For Release.....	5,984	Tests
Inspection Samples.....	1,193	"
Complaint Investigations.....	29	"
Total	7,206	"

The data obtained served as the bases of recommendations for acceptance or rejection of the individual lots examined.

In addition 1,386 cooperative service tests were done on biological products not licensed.

(b) A permanent record and filing system for releases, protocols of manufacturers' tests and samples of all biological products submitted to the Division of

Biologics Standards was maintained. During the same period indicated above 4,894 lots of biological products were submitted for release by licensed manufacturers. Of these 4,848 lots were released, 12 lots were rejected and 34 lots were withdrawn from consideration for release by the manufacturers.

(c) Conducted 8 complaint and 9 special investigations on biological products and matters related to control activities during the year. Reports and recommendations for action were made to the Chief, Laboratory of Control Activities.

(d) Quality control evaluations were made during the year of data collected in official potency tests run on cholera vaccines, rabies vaccines, smallpox vaccines, typhoid vaccines, and poliomyelitis immune globulins (Lansing antibody titrations). Charts were made plotting the respective endpoint reactions obtained with the NIH reference materials in the various tests. Results showed that most of the potency assays conducted over the past several years fell within 2 standard deviation limits.

This information has been helpful in studying variable factors in the test systems, in considering possible modifications or improvements in the laboratory control methods, and in keeping check on the continued stability and effectiveness of official reference standards.

II. Research

In addition to the above control testing, 45 research experiments were carried out during the year in connection with the various projects underway. Brief summaries of these studies are given as follows:

(a) A collaborative inter-agency project with members of Walter Reed Army Institute of Research involving laboratory and clinical studies to determine the stability and effectiveness of dried calf lymph smallpox vaccine was continued during the year. Potency experiments were run after 82, 91, 99 and 113 weeks of storage on samples of dried vaccine stored at varying temperatures.

After 18 months storage and testing, reevaluation of the data was made and a progress report was prepared. The rabbit scarification data at this point showed unsatisfactory potency levels for dried vaccine kept at +56°, +45°, +37°C after 2, 8, and 12 week storage periods respectively, whereas, vaccine stored at lower temperatures maintained its infectivity for rabbits for at least 12 months at +22°C and for 18 months at both +4° and -20°C.

Human trials and assays by pock counting and plaque counting techniques have not reflected any significant changes in infectivity of those vaccines stored at -20°C, +4°, and +22°C for an 18 month period. Dry vaccine held at 56°C for 12 weeks was shown to be effective in vaccinating man when compared to liquid glycerinated vaccine normally issued to the Military, even though it did not show an acceptable degree of potency when measured on the rabbit skin. These data have been most useful in recent considerations concerning the licensing of dried smallpox vaccine of calf lymph origin and in a revision of dating requirements for this product. It is still anticipated that the Military will initiate some joint report for publication following completion of the stability studies.

In addition to the above studies, potency assays by rabbit scarification technique were run on 3 experimental lots of dried smallpox vaccine of chick embryo chorioallantoic membrane origin for the Military. These lots failed to meet the NIH minimum potency requirements and were reported as unsatisfactory.

(b) Two manuscripts on studies carried out with smallpox vaccines have been completed during the year. These papers were submitted to the Editor, Bulletin of the World Health Organization and have been accepted for publication. (See Part B of the report for publications).

(c) The cooperative study on the development and standardization of a reference diphtheria toxin for the Schick test was continued during the year. Specifications for a freeze-dried preparation to be used as the official U. S. standard were drawn up in cooperation with Dr. E. B. Seligmann and Dr. M. Barile and a lot of the material was processed under commercial laboratory conditions. Efforts are now underway to complete this study. It is anticipated that the work in progress will proceed according to the following program:

(1) Pilot studies involving potency (MRD and MLD) and the

antitoxin combining (Lr) determinations on random sampled vials of the lot of the standard Schick toxin.

(2) Comparative testing of the U. S. Standard to the WHO Standard Schick Toxin.

(3) Evaluations of commercial Schick toxins by the proposed potency test which incorporates the use of the U. S. Standard Schick Toxin.

(4) Preparation of a proposed draft of additional standards for Diphtheria Toxin for the Schick Test.

(5) Submission of the proposed method of potency assay and the U. S. Standard Schick Toxin to the manufacturers for trial and comment.

(6) Preparation and presentation of experimental data to a scientific journal for publication.

(d) A collaborative study was initiated with Dr. E. B. Seligmann, Reference Standards Section, Laboratory of Control Activities, on the standardization of an official NIH Reference Smallpox Vaccine. Specifications were drawn-up and a dried lot of vaccine of calf lymph origin was obtained from a licensed manufacturer for adoption as the standard preparation. Experiments have been initiated to compare the potency of the proposed standard to that of the Current NIH Control Vaccine, Lot 1b as measured by the official rabbit scarification technique. It is planned that subsequent evaluations will include:

(1) Studies to determine stability of the standard vaccine under varying conditions of storage.

(2) Experiments to determine variability of potency among ampules from different drying runs.

(3) Comparisons of the standard with the current house references used by licensed manufacturers.

(4) The use of the reference vaccine on human subjects in order to correlate its clinical effectiveness with that determined by laboratory means.

(5) Establishment of official regulations for the control of smallpox vaccine based on the use of an official physical standard.

(e) Studies were resumed on methods of potency assay for the

fluid diphtheria component of Tetanus and Diphtheria Toxoids Combined (For Adult Use) in order to extend standards to cover this product. In cooperation with Dr. E. B. Seligmann efforts were directed toward the development of a fluid reference diphtheria toxoid and a reference diphtheria toxin for use in these potency assays. Results of experimental data to date have led to the preparation of a tentative draft of requirements for the product, which has been submitted to licensed manufacturers for review and comment.

(f) Contributed to a study concerning antibody response in patients with acute leukemia conducted by Dr. Richart T. Silver, General Medical Branch, National Cancer Institute and Dr. John P. Utz, Laboratory of Clinical Investigations, National Institutes of Allergy and Infectious Diseases. The results of this study were published during the current year. (See Part B of the report for publication).

III. Supportive Control Activities

(a) During the current year, numerous new establishment and product applications were submitted for consideration for license. Usually these are referred to committees for prescreening and careful review for compliance with regulations and requirements. This laboratory was involved in a number of such actions during the year. Also, involved is the control testing of the products submitted in support of license application. Complete reports and recommendations were made following review of 10 establishments and 23 product license applications during 1960.

(b) Participated in the annual inspection program of biological establishments by carrying out 1 special, 1 prelicensing, and 26 regular inspections. Official reports and recommendations were made on all establishments visited.

(c) Prepared new and revised requirements for Tetanus and Diphtheria Toxoids Combined (For Adult Use). Assisted in the formulation of regulations for allergenic extracts for the sterility testing, pyrogen testing and dating of biological products.

(d) Thirteen visitors representing 10 foreign countries were given orientation and training in control testing and related activities during 1960. The length of the visitations ranged from several hours to 3 days.

IV. Proposed Course of Project

The proposed course is to continue the control testing, research and related objectives with increasing efficiency and attempt to reach conclusions on research projects in as satisfactory and expeditious manner as possible. Also, it is the intent of this laboratory to possibly engage in the following additional study:

(1) A collaborative study on the stability of the Diphtheria Toxin Standard For Schick Testing under varying conditions of storage.

Serial No. DBS 3
1. Control Activities
2. Control Tests
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B.

Publications:

1. Silver, Richard T.; Utz, John P.; Fahey, John; and Frei, Emil III. With technical assistance of Kolb, Robert; Kassel, Julius A.; and Szwed, Clarence.

   Antibody Response In Patients With Acute Leukemia. Journal of Laboratory and Clinical Medicine 56 (4): 634-643; 1960.

2. Kolb, Robert W.; Cox, Claire B.; and Aylor, Harry T.

   Improvements in the Rabbit Scarification Technique for the Potency Assay of Smallpox Vaccine. Bulletin of the World Health Organization - In Press.

3. Kolb, Robert W.; Cutchins, Ernest C.; Jones, Wm. P.; and Aylor, Harry T.

   A Comparison of the Rabbit Scarification Technique with Titrations in Cell Cultures for the Potency Assay of Smallpox Vaccine. Bulletin of the World Health Organization - In Press.

Serial No. DBS 4
1. Control Activities
2. Pyrogens
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Section on Pyrogens

Principal Investigator: Harry W. Burruss

Other Investigators: None

Cooperating Units: None

Man Years
Total: 2 1/2
Professional: one
Other: 1 1/2

Patient Days: None

Project Description:

The primary responsibility of this section is the testing of certain licensed biological products to determine their safety, purity, and stability as defined in the control regulations under the Public Health Service Act. These biological products, especially the blood products of human and animal origin, are tested for pyrogenicity; their purity is determined in part by total solids content; and moisture determinations are made as a measure of stability of dried products. The principal products for pyrogen testing, which are submitted by licensed manufacturers for release, include streptokinase-streptodornase, vaccines, antivenins, antitoxins, blood albumin, globulin, fibrinogen, fibrinolysin, plasma, and serums.

A total of 963 samples were tested for pyrogenicity during the year which required the use of approximately 2900 rabbits. This figure includes 77 samples from the Laboratory of Blood and Blood Products and 315 pharmaceutical preparations from the NIH Clinical Center Pharmacy. Studies were made to determine the test dose in rabbits on the pharmaceutical products for which no pyrogen test dose had been established.

All pyrogen test results reported in the manufacturers' protocols to the Laboratory of Control Activities were evaluated. On the basis of these evaluations and additional DBS tests on samples of the product submitted, recommendations for release or rejection were made. Records of all tests were maintained and officially reported.

Twenty pharmacy students from George Washington University and 10 visiting scientists from domestic and foreign health laboratories and from licensed biological establishments were shown the techniques used in performing the work of this section. The chief of this section also assisted in the annual inspection program of several licensed manufacturers and served on a committee to make a recommendation on the suitability of a lot of yellow fever vaccine secondary seed virus proposed for use by a licensed manufacturer.

Samples of each lot of Normal Human Serum Albumin released by the Laboratory of Control Activities continue to be distributed to different hospitals for clinical testing. Reports received on these lots of albumin confirm the reliability of the pyrogen test as a means of determining the safety of the product.

Control work in this section involves studies designed to adapt the above mentioned tests to new products, to study the factors influencing the test, and the adaptability of these tests as a means of evaluating the safety of experimental pharmaceuticals, including radioactive isotopes, under development by the NIH Pharmacy Department for clinical study in the NIH Clinical Center.

Most of the work has been completed in setting up the equipment necessary to change over the hand-thermometer-lap-method of handling rabbits used in the pyrogen test to a semi-automatic method with an electric thermometer and thermocouples which will increase the efficiency of the operation.

Part B included Yes / / No / X /

Serial No. DBS 5
1. Control Activities
2. Reference Standards
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Investigations Related to the Establishment and Maintenance of Reference Standards for Biological Products.

Principal Investigator: E. B. Seligmann, Ph.D.

Other Investigators: E. C. Russell

Cooperating Units: None

Man Years
Total: 4
Professional: 1
Other: 3

Patient Days: None

I. Project Description:

Objectives: Since biological products cannot be standardized, with few exceptions, by chemical or physical means, recourse must be had to testing their effects in relation to physical reference preparations. It is the function of this project to provide these standard preparations for the use of manufacturers and others engaged in standardization. In this way uniformity of potency is established throughout the country. It is largely by the use of these standards that those portions of the biologics law relating to potency can be enforced. A great deal of painstaking and responsible work is necessary to insure that standards issued are satisfactory as official standards for this country and bear a known relation to International Standards.

Methods Empolyed: Fluid preparations must be made and standardized from dried primary standards prior to the expiration date of the current lot. Old standards must be replaced as they become exhausted. Standards must be developed for new products and for certain of the older ones for which it has not been possible to prepare standards heretofore. This is dependent upon advanced knowledge in a number of fields, such as immunology, biology, biochemistry, and medicine. Important features of this work are the

improvement of methods of preserving and storing standards, such as by freezing and drying, so that their potency may be maintained, selection or development of standard preparations which will yield clear-cut end points in control testing done by all manufacturers, and correlation of these standards where possible with those established in other countries or with International Standards.

Major Findings and Accomplishments:

(a) In order to maintain an adequate supply of physical reference standards for use by the licensed manufacturers in their official control testing it is necessary to prepare and standardize new liquid lots from the primary dried stocks. The number of lots prepared and standardized during the year were antitoxins - 12, serums - 2, vaccines - 5, and toxoids - 6. A total of 112 tests were required to complete a satisfactory standardization of these lots. These tests include flocculation reactions, animal protection tests, animal potency tests, neutralization tests, and a number of specialized tests for specific products.

(b) Standard and Reference preparations and cultures are freeze-dried for greater stability during storage. This Section dried the following between January 1, 1960 and December 9, 1960:

Cultures	2200 ampules
Serums	675 ampules
Vaccines	1015 ampules
Viruses	717 ampules
Toxins	274 ampules

(c) This Section distributed to commercial houses, health departments, universities, and foreign countries the following Standard and Reference preparations:

Antitoxins	337
Serums	1635
Vaccines	1655
Toxins	126
Cultures	462
Viruses	268

(d) A culture collection of organisms used in the production and testing of biological products

is maintained by this Section. Official Standard, Reference and Control preparations currently maintained are:

1. Standard Preparations

Bacterial Products

Botulinus Antitoxin, Type A
Botulinus Antitoxin, Type B
Diphtheria Antitoxin
Dysentery Antitoxin (Shiga)
Histolyticus Antitoxin
Oedematiens Antitoxin
Perfringens Antitoxin (Welchii)
Pertussis Vaccine
Opacity Standard for Pertussis Vaccine
Opacity Standard for Typhoid Vaccine
Scarlet Fever Streptococcus Antitoxin
Sordelli Antitoxin
Staphylococcus Antitoxin
Tetanus Antitoxin
Old Tuberculin
PPD of Tuberculin
Vibrion Septique Antitoxin

Viral Products

Antirabies Serum

Blood Products

Thrombin

2. Reference Preparations

Bacterial Products

Botulinus Antitoxin, Type C
Botulinus Toxin, Type A
Botulinus Toxin, Type B
Cholera Opacity Reference
Diphtheria Toxoid (AP)
Diphtheria Toxoid (Fluid)
Diphtheria Flocculating Serum
Haemophilus influenzae Typing Sera, Types a,b,c,d,e,f
Histolyticus Toxin
Histoplasmin
Nitrogen Reference
Oedematiens Toxin

Perfringens Toxin
Plague Vaccine
Tetanus Toxoid (AP)
Tetanus Toxoid (Fluid)
Tetanus Flocculating Serum
Typhoid Vaccine
Typhoid Turbidity Reference

Viral Products

Adenovirus Vaccine Types 3,4,7
Adenovirus Crude Fluid, Type 3, Strain JF
Influenza Virus Vaccine
Mumps Serum
Poliomyelitis Immune Globulin
Poliomyelitis Serum
Poliomyelitis Vaccine, Type 1,2,3
Poliomyelitis Virus, Type 1
Rabies Vaccine
Rabies Challenge Virus
Rabies Production Virus
Smallpox Vaccine
Typhus Serum

Blood Products

Anti-A Blood Grouping Serum
Anti-B Blood Grouping Serum
Anti-Rh_o (Anti-D) Typing Serum
Coomb's Anti-Human Serum
Fibrinogen

3. Control Preparations

Bacterial Products

Antimeningococcic Serum
Hemophilus Influenzae Antiserum, Type b
Scarlet Fever Streptococcus Toxin
Sordelli Toxin
Staphylococcus Toxin
Tetanus Toxin
Vibrion Septique Toxin

(e) Yellow Fever Vaccine manufactured under U. S. Government license has been tested for conformance to the official regulations governing its production. A total of 273 lots were tested for safety, potency, and purity during the year.

(f) A Total of 204 ampules of Opacity Standard for Pertussis Vaccine was prepared and submitted to the World Health Organization for consideration as an International Standard.

(g) The Section took part in a collaborative assay of Yellow Fever Vaccine with the Institute for Tropical Hygiene, Amsterdam; Wellcome Research Laboratories, Beckenham; and Robert Koch Institute, Berlin. The study was initiatiated by the World Health Organization to determine the acceptability of Yellow Fever Vaccine produced by Robert Koch Institue for use in immunization for international travel.

(h) Assisted in the control inspection program by conducting eighteen annual inspections and three special or per-license inspections during the year.

(i) In collaboration with Mr. Kolb the rewriting of the Minimum Requirements for antitoxins and toxoids in the form of Regulations was initiated. As a member of a committee assisted in the writing of Additional Standards for Allergenic Extracts. Consulted with Dr. Hottle and Dr. Van Hoosier in the rewriting of the Minimum Requirements for Yellow Fever Vaccine in the form of Regulations.

II. Proposed Course of Project:

An active research progeam has been initiatiate to provide basic data on the properties of existing and new standard preparations. A program designed to maintain a continuing, evaluation of the stability of each physical standard preparation has been established. A program to gradually improve existing preparations if improvement is necessary has been started. During the year one preparation has been replaced with a better one and work is in progress on three others. Establishment of physical standards for products not now provided with an official standard for the potency test has been started with research on a Reference or Standard Smallpox Vaccine.

III. Proposed Projects:

Continuation of projects already in progress.

IV. Projects in Progress:

(a) Standardization of a Smallpox Vaccine for use as an official standard in collaboration with Mr. R. W. Kolb.

(b) Development of a Reference Diphtheria Toxoid for use in the potency test for the fluid Tetanus and Diphtheria Toxoids Combined (For Adult Use).

(c) Studies on the light and dye inactivation of rabies virus in collaboration with Dr. C. W. Hiatt.

(d) Development of an official potency test for Scorpion Antivenin.

(e) Development of a dried Poliomyelitis Vaccine in collaboration with Dr. W. B. Uhlendorf, Viral Immunology Laboratory.

Part B included Yes / / No / X /

Serial No. DBS 6
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Pertussis Vaccine

Principal Investigator: Dr. Margaret Pittman

Other Investigators: Mr. Howard Bohner
Dr. John C. Feeley

Cooperating Units: None

Man Years:

Total:	1.9
Professional:	0.9
Other:	1.0

Project Description:

Objectives: The objective is that all lots of pertussis vaccine processed by U. S. licensed establishments have optimum properties: adequate in potency, stable in potency throughout the dating period and relatively free from untoward reactive substances.

Methods Employed: 1. The potency and toxicity of the pertussis component of all lots of products containing this antigen are kept under constant surveillance by reviewing protocols and license applications submitted by manufacturers, by conferences with representatives from manufacturers, by testing the majority of the lots submitted (about 200 per year) for potency and freedom-from-toxicity. International correspondence and exchange of material to keep abreast of international progress and control measures.

2. Special study on the stability of the potency of pertussis vaccine in quadruple antigen vaccine.

3. Study of the specific sensitizing property of pertussis vaccine and attempts to determine if this property is related to the toxicity of the vaccine.

Major Findings: Although the majority of lots of pertussis vaccine continue to be satisfactory in required properties, variation in potency and freedom-from-toxicity continue to appear with changes in methods of preparation and use in new products.

Significance to the Program of DBS: (1) The surveillance of pertussis vaccine provides information relating to control and improvement of the product.

(2) In a brief published statement, it was alleged that the potency of the pertussis vaccine component in quadruple antigen vaccine was not stable throughout the dating period. The results of the present study should enable the Division to determine whether or not there is any validity in the statement.

(3) Basic information about the specific sensitizing properties and the toxicity of vaccines prepared by different methods provide information relative to the improvement of the product.

Proposed Course of the Project: To continue as outlined above and to publish a statement on stability of pertussis vaccine when work of item 3 has been completed.

Part B included Yes / / No /X/

Serial No. DBS 7
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Typhoid Vaccine

Principal Investigator: Dr. Margaret Pittman

Other Investigator: Mr. Howard Bohner

Cooperating Units: Expert Committee on Biological Standardization, World Health Organization

Man Years:

Total:	0.6
Professional:	0.3
Other:	0.3

Project Description:

Objectives: The objectives of the WHO Project are to determine the protective activity of typhoid vaccine for man and to correlate field trial results with a laboratory measurement of potency. Two large lots of vaccines have been prepared by WRAIR. These are being used in field trials in three countries and a number of laboratories are cooperating in the laboratory evaluations. Our laboratory is participating in the latter phase.

Methods Employed: Methods outlined by WHO are being followed. These consist of (1) the immunization of rabbits by two schedules and the titration of the H, O, and Vi antibody responses and (2) an active protection test in mice in which the cultural challenge is suspended in saline. The U. S. Reference typhoid vaccine is being tested concurrently with the two WHO lots. In addition all three lots are being tested by the U. S. required mouse protective potency test in which the cultural challenge is suspended in a mucin preparation.

Significance to the Program of DBS: It is hoped that concrete information will be obtained in the WHO Project that can be applied directly to the control and perhaps improvement of typhoid vaccine produced by U. S. licensed establishments.

Part B included Yes [ ] No [X]

Serial No. DBS 8
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Participation in Establishment of Pakistan-SEATO Cholera Research Laboratory and Conference on Cholera

Principal Investigator: Dr. John C. Feeley

Other Investigator: Dr. Margaret Pittman

Cooperating Units: NIH Cholera Advisory Committee

Man Years:

Total:	0.25
Professional:	0.25
Other:	0.0

Project Description:

Objectives: Participation in establishment of the Pakistan-SEATO Cholera Research Laboratory in Dacca.

Methods Employed: Selection of equipment, which was shipped from NIH, and setting up of this equipment in the Pakistan-SEATO Cholera Research Laboratory. This involved a 2-month tour of duty in Dacca. Also participated in the First Conference on Cholera sponsored by SEATO International Committee on Cholera Research.

Significance to the Institute: Establishment of this modern laboratory facility in an area where cholera is endemic should offer numerous opportunities for productive research findings in cholera and other enteric diseases. Of particular significance to DBS is the possibility of carrying out a field trial of cholera vaccine in connection with this project.

Proposed Course of the Project: To follow through as indicated.

Part B included Yes [X] No [ ]

Serial No. DBS 8

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications:

Presentation of a paper

Feeley, J. C. and Pittman, M. A mouse protective test for assay of cholera vaccine--at the Conference on Cholera, Dacca, East Pakistan, December 5 - 8, 1960.

Serial No. DBS 9
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Study of Cholera and Other Vibrios Isolated in Bangkok, 1959-1960

Principal Investigator: Dr. John C. Feeley

Other Investigators: None

Cooperating Units: Thailand-SEATO Cholera Research Laboratory
Jefferson Medical College
University of Chicago
Walter Reed Army Institute of Research
Pasteur Institute

Man Years:

Total:	0.6
Professional:	0.3
Other:	0.3

Project Description:

Objectives: This project was initiated as part of a program to confirm the identification of strains of Vibrio comma isolated at the Thailand-SEATO Cholera Research Laboratory not only from cases of clinical cholera, but also from patients with mild diarrhea, "contacts," food, and water.

Methods Employed: This study in a large part has involved use of conventional bacteriologic and serologic procedures. Cultures received from Bangkok were freeze-dried with a minimum of delay in order to maintain, insofar as possible, their original characteristics. From NIH, cultures were distributed for independent study in freeze-dried form to Walter Reed Army Institute of Research, Dr. Kenneth Goodner (Jefferson Medical College, Philadelphia), Dr. William Burrows (University of Chicago), and Dr. J. Gallut (Pasteur Institute, Paris).

Major Findings: A total of 94 cultures were received and subjected to study. Fifty-nine were submitted as either Ogawa or Inaba type strains of V. comma. Nine proved nonagglutinable in cholera immune serum and thus could not be identified as bonafide

cultures of V. comma. The remaining 50 presumptive cholera cultures were considered to possess attributes consistent with positive identification as strains of V. comma. However, 2 of 19 cultures submitted as Ogawa type appeared to belong to the Inaba subgroup, while 5 out of 40 cultures submitted as Inaba type reacted as Ogawa.

Significance to the Institute: The isolation of apparently typical cultures of Vibrio comma from mild diarrheas, "contacts", food, and water is a matter of considerable epidemiologic significance requiring thorough verification. The findings of the Thailand-SEATO Cholera Research Laboratory may contribute important information not only on the means of transmission, but also on the apparently enigmatic manner in which the organism survives in interepidemic periods. The present findings confirming the identification of most of the alleged strains of V. comma should help establish the Bangkok work on a firm footing. When combined with results from other laboratories studying these cultures, a rather complete picture of the properties of these Vibrio cultures should be available.

Proposed Course of the Project: Bacteriologic studies on these cultures have been, for the most part, completed. This laboratory will continue to serve as a depository for these cultures. Results obtained in the study will be combined with independent observations in other laboratories.

Part B included Yes / / No /X/

Serial No. DBS 10
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Re-evaluation of Requirements for Cholera Vaccine

Principal Investigator: Dr. John C. Feeley

Other Investigators: None

Man Years:

Total:	1.0
Professional:	0.5
Other:	0.5

Project Description:

Objectives: The objectives of this project are the investigation of methods for assaying the potency of cholera vaccine and establishment of an improved U. S. Standard of Potency for this product. It is anticipated that this study will be coordinated with proposed WHO efforts toward establishment of a meaningful potency standard related to prophylactic efficacy in man.

Methods Employed: Much of the present effort has been directed toward elucidating the numerous experimental variables involved in performance of a quantitative active protection test in mice.

Work to date has been based on liquid monovalent experimental reference vaccines of commercial origin. A comparison of the potency of these vaccines with the corresponding freeze-dried WHO International Reference Preparations has been made. Considerable attention is being devoted to the problem of establishing stable freeze-dried Ogawa and Inaba reference preparations. Technical details relative to preservation of potency during freeze-drying are currently under study. In connection with this aspect of the problem, work is in progress to evaluate the effect of different killing agents and preservatives on potency and stability of liquid and freeze-dried vaccines.

Studies related to evaluation of the immune response to cholera vaccine as agglutinating, bactericidal and mouse protective antibodies are also being pursued with a view to correlating this information with active mouse protection data.

Major Findings: As reported previously, an active mouse protection test procedure has been developed which offers a reasonable degree of reproducibility and which expresses potency relative to a reference vaccine. Although experimental liquid reference vaccines employed in this work have apparently remained stable since manufacture approximately 2 years ago, reference preparations should ideally be stored in a form less subject to deterioration. A rather alarming fall in mouse protective potency has been observed when ordinary commercial (phenolized) cholera vaccine is freeze-dried. In several experiments a 10-fold or greater drop has occurred. Phenol appears to be deleterious during the freeze-drying process if the vaccine contains the usual 0.5 percent concentration.

Studies comparing the mouse protective potency of NIH experimental liquid reference vaccines with the corresponding freeze-dried WHO International Reference Preparations indicate the former to be much more potent, although made from the same vaccine strains and containing the same concentration of bacteria. The NIH experimental Ogawa reference was 8.5 times, and the NIH experimental Inaba reference 34 times, as potent as the corresponding WHO International References. It is felt that the lower potencies of the WHO preparations may be related to loss during freeze-drying.

Studies to evaluate the effects of different killing agents and preservatives on potency and stability have not progressed sufficiently for full evaluation at this time. However, preliminary evidence indicates that living cholera vibrios are considerably more immunogenic than vibrios killed by heat, merthiolate, formalin, or phenol.

Work on measurement of the immune response to cholera vaccine in terms of agglutinating, bactericidal, and mouse protective antibodies has been chiefly related to the technical aspects of the problem. Bactericidal antibody titrations appear to offer the greatest promise of being useful in vaccine assays, but a thorough comparison of all these indices of antibody response may prove helpful in evaluation of potency in parallel with active mouse protection tests.

Significance to the Institute: Concrete information is still generally lacking on the effectiveness of cholera vaccine in protecting against human infection. The currently required method for potency testing is generally accepted as being quantitatively inadequate. It now seems possible to obtain quantitative laboratory data on vaccine potency by *in vivo* and *in vitro* assays. However, only when these laboratory results are related to prophylactic efficacy in man can a meaningful standard of potency be developed.

Proposed Course of Project: Work on establishment of reference vaccines will be continued, as well as various technical problems in quantitating the immune response. The application of quantitative laboratory procedures for vaccine assay can then be carried out, hopefully, in connection with field trial data, in establishment of a realistic U. S. Standard of Potency.

Part B included Yes / / No /X/

Serial No. DBS 11
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Urinary blood group substance

Principal Investigator: Dr. Harold Baer

Other Investigator: Dr. Allan Kliman

Cooperating Unit: Laboratory of Blood and Blood Products

Man Years:

Total:	1.25
Professional:	0.75
Other:	0.5

Project Description:

Objectives: To determine whether the A, B, O blood group substance is present in urine as regularly as in other body fluids and whether this activity can be measured with sufficient simplicity to permit its use in blood grouping of individuals if blood was not readily available.

Methods Employed: The test for inhibition of hemagglutination was employed using washed human erythrocytes, anti-A and anti-B sera, and Ulex europeus extract. Urines were tested directly and following concentration. Urine and saliva from normal individuals as well as those with various diseases were compared.

Major Findings: The blood Group A and B activity of urine could be determined directly and was always present when the saliva possessed this activity. The O (H) activity of urine could only be measured following concentration and was only found in specimens from individuals of Group O. In this respect urine was markedly different from saliva since the latter could effect inhibition of Ulex extract without concentration and without regard to the A, B, O blood group of the individual. Disease status, to the extent studied, did not alter the reaction.

Significance to the Institute: This procedure may provide the blood bank with a useful means of blood grouping individuals when

blood is not readily available.

Proposed Course of Project: Publication.

Part B included Yes / / No /X/

Serial No. DBS 12
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Studies on the Specificity of Tuberculins

Principal Investigator: Dr. Harold Baer

Other Investigator: Dr. Sotiros D. Chaparas

Cooperating Units: None

Man Years:

Total:	1.0
Professional:	0.75
Other:	0.25

Project Description:

Objectives: Attempts to improve the specificity of tuberculins.

Methods Employed: Analyses of the antigenic complexes of the various mycobacteria are being performed with the aid of gel-diffusion techniques, immuno-electrophoresis, guinea pig skin tests and chemical fractionations including column chromatography. In this way it is hoped to isolate and identify highly specific substances capable of eliciting delayed hypersensitivity reactions.

Major Findings: As many as 9 bands of precipitate were noted when BCG culture filtrate antigens diffused toward homologous antibody in gel-diffusion tests. At least 3 precipitin bands were found with culture filtrates of Mycobacterium balnei and Mycobacterium pisceum using antibody to BCG tuberculoprotein in the gel-diffusion test. Further resolution of the BCG antigens was accomplished with immuno-electrophoresis.

Significance to the Institute: The isolation of substances capable of eliciting delayed skin reactions, specific to species or strains of mycobacteria should provide an opportunity to establish reliable standards for antigens used in skin testing.

Proposed Course of Project: Sensitization of guinea pigs with a number of mycobacterial strains, later testing these animals with the various fractions prepared by the methods described above.

Part B included Yes [ ] No [X]

Serial No. DBS 13
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: The Schick Test Toxin (Diphtheria)

Principal Investigator: Dr. Michael F. Barile

Other Investigators: Mr. Donald B. Riggs
Mr. Robert W. Kolb (LCA)

Cooperating Unit: Section on Control Test, Laboratory of Control Activities

Man Years:

Total:	1.6
Professional:	0.8
Other:	0.8

Project Description:

Objectives: A. 1. To select a diphtheria toxin for the U. S. Standard for the Schick Test. 2. Re-evaluate the requirements of the Schick test with reference to a more accurate potency assay. B. To determine the amount of immunity necessary in guinea pigs to cause a Schick negative reaction.

Methods Employed: A. Determination and characterization of biologic properties of two toxin preparations were made. On the basis of intradermal toxicity, lethality, in vivo toxin antitoxin, combining ability and combining velocity in guinea pigs and rabbits, a toxin preparation was selected as a diphtheria reference. The toxin was freeze-dried with several different menstruum to determine the most stable system to be used for this procedure. Specifications for the freeze-dried preparation were drawn and a lot of the toxin was processed under commercial laboratory conditions. The dried U. S. Standard Diphtheria Toxin for the Schick Test is currently under examination to determine: 1) potency (MRD and MLD) and antitoxin combining (Lr), 2) comparison to the WHO International Standard, 3) evaluation of the proposed potency test for commercial

toxin preparations which incorporates the U. S. Standard as a reference, and 4) the stability of the toxin standard.

B. Guinea pigs were immunized with commercial diphtheria toxoid preparations. After 6 weeks, the sera from each animal were tested for units of diphtheria antitoxin and these findings were compared to the number of Schick test doses of toxin the corresponding animal could neutralize when challenged by intradermal inoculation.

Major Findings: B. Animals immunized with one-half a human dose of diphtheria toxoid had from 1 - 5 units of circulatory antitoxin/ml and could neutralize no less than 1,000 Schick test doses of diphtheria toxin intradermally. By extrapolation the guinea pig could neutralize one Schick dose if 1/1000 or more units of antitoxin were made available at the inoculation site.

The Proposed Course of Project: The proposed course of study includes: A. 1) Revision of standards for Diphtheria Toxin for the Schick Test, 2) Submission of the revised standards and the proposed U. S. Standard Diphtheria Toxin to the manufacturers for trial and comment and 3) presentation of data for publication.

Part B included Yes / / No /X/

Serial No. DBS 14
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Pleuropneumonia-like Organisms from Tissue Culture

Principal Investigator: Dr. Michael F. Barile

Other Investigators: Mr. Donald Riggs
Dr. Casper Hiatt (LBB)
Major Walter F. Malizia (AFIP)

Cooperating Units: Laboratory of Biophysics and Biochemistry
Armed Forces Institute of Pathology

Man Years:

Total:	0.2
Professional:	0.1
Other:	0.1

Project Description:

Objectives: To develop methods of detecting and purifying the LVP tissue culture lines contaminated with PPLO and/or L forms of bacteria by the a) fluorescent antibody technique and by b) use of the photoinactivation procedure.

Methods Employed: a) The fluorescent antibody technique was used to determine the antigenic structure of PPLO isolated from tissue culture. Specificity of the fluorescent antibody reaction was examined by testing it with human PPLO strains and various bacterial species. b) The photoinactivation procedure was used to determine the effect on the viability of PPLO strains in suspension and in contaminated tissue culture cells.

Major Findings: a) Fluorescent antibody prepared against a tissue culture PPLO strain reacted specifically with tissue culture cells contaminated with tissue culture PPLO strains but not with other PPLO strains or with 24 different bacterial species. b) Preliminary findings indicate that PPLO are sensitive to the action of photoinactivation, when tested in broth suspension.

Proposed Course of Project: Several more PPLO strains shall

be tested. Attempts shall be made to determine whether tissue culture cells contaminated with PPLO can be purified by the photo-inactivation procedure.

Part B included Yes /X/ No /___/

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications.

Publications other than abstracts from this project:

1. Barile, M. F. and Sheingorn, A. The Isolation and Cultivation of a Filterable Form Resembling Pleuropneumonia-like Organisms from the Human Dental Pulp. Oral Surgery, Oral Medicine and Oral Pathology 13(6): 756-760, 1960.

2. Malizia, Walter F., Barile, Michael F., and Riggs, Donald B. Immunofluorescence of Pleuropneumonia-like Organisms Isolated from Tissue Cell Culture. Nature (In press).

Serial No. DBS 15
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Staphylococcal Products

Principal Investigator: Dr. Michael F. Barile

Other Investigator: Mr. Donald B. Riggs

Cooperating Units: None

Man Years:

Total:	0.2
Professional:	0.1
Other:	0.1

Project Description:

Objectives: To reevaluate and develop reliable procedures for the evaluation of potency, purity and safety of biologic products derived from Staphylococcus aureus.

Methods Employed: In vivo and in vitro immunological methods will be used in studying the activity of staphylococcal products including phages for human administration.

Significance to the Institute: In view of the renewed interest in staphylococcal products for both immunization and therapy, the present study will provide background information for the reevaluation of the present requirements for the currently licensed products and for the evaluation of new products that may be developed.

Part B included Yes [ ] No [X]

60

Serial No. DBS 16
1. Viral Immunology
2. Section on Testing
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Functions Associated with the Poliomyelitis Vaccine Safety Testing Program.

Principal Investigator: Dr. Samuel Baron

Other Investigators: Dr. Robert Friedman
Dr. Ruth Kirschstein
Dr. George A. Hottle
Dr. B. William Uhlendorf
Dr. C. W. Hiatt
Dr. Gerald L. Van Hoosier
Dr. G. Borman
Dr. F. Perkins

Cooperating Units: None

Man Years:
Total 3-1/2
Professional 1
Other 2-1/2

Sub-project A: Concentration of Poliomyelitis Vaccine and the Sensitivity of the Monkey Safety Test.

Objective: To increase the sensitivity of the monkey safety test by increasing the effective volume tested in monkeys.

Methods Employed: Studies were continued in which experimentally infected poliomyelitis vaccines were concentrated 100-fold by the ultracentrifuge-gelatin method developed in this laboratory. The concentrate is inoculated intraspinally in one group of monkeys and unconcentrated material was inoculated into an equivalent group of monkeys. Comparison of paralytic rates, pathological findings and virus isolations was made between the two groups.

Major Findings: Monkeys inoculated with concentrated experimental vaccines were infected with poliovirus more frequently than those monkeys inoculated with equivalent but unconcentrated material. The increased infectivity was correlated with the degree of concentration. This monkey safety test using concentrated vaccine was more sensitive or at least equally sensitive to poliovirus in experimental vaccines than was the monkey kidney cell culture test when equal volumes of vaccine were used.

Significance to the Division: The use of concentrated vaccine in the monkey safety test appears to be the most sensitive technique developed for the detection of residual live virus in poliomyelitis vaccine.

Proposed Course: To write the results for publication.

Sub-project B: Sensitivity of Cell Cultures to Poliovirus.

Objective: To control sensitivity of cell cultures used for the poliomyelitis vaccine tissue culture safety test.

Methods Employed: Poliovirus is titrated in each cell lot both before and after use in the vaccine test. Only cell lots with maximum sensitivity are approved for use in the test. Serums which may be used in the cell culture system, are tested for poliovirus inhibitors. Only inhibitor-free serums are approved.

Major Findings: The great majority of cell cultures have been determined to be highly sensitive to poliovirus and therefore suitable for the safety test. Also some calf serum lots have been selected for use after demonstration of lack of poliovirus inhibitor.

Significance to the Division: Provides control of sensitivity of poliomyelitis vaccine cell culture test.

Proposed Course: This control activity to continue.

Sub-project C: Isolation and Virulence Characterization of Attenuated Live Poliovirus from Stools of Vaccine Recipients and from Monkey Tissues.

Objective: To evaluate virulence and capacity to revert to virulence of live poliovirus vaccine strains.

Methods Employed: Isolation of virus from stool or tissues followed by characterization of virulence by *in vitro* genetic markers and *in vivo* monkey virulence.

Major Findings: The relative virulence of various proposed vaccine strains has been determined. Also some of these strains were shown to revert towards virulence by in vitro markers after passage through the human intestinal tract. There may be a correlation between in vitro findings and in vivo virulence.

Significance to the Division: Provides information relative to selection of suitable strains for live poliovirus vaccine.

Proposed Course: Continue evaluation of reversion to virulence by poliovirus in human stool specimens. Correlate virulence in man with virulence in monkeys and with virulence as determined by in vitro markers.

Subproject D: Study of poliovirus inhibitor in the central nervous system of monkeys.

Objective: To characterize and determine methods for eliminating an interfering poliovirus inhibitor which was discovered in the nervous system of rhesus monkeys and to evaluate its importance in disease.

Methods Employed: Suspension of nervous tissue is mixed with poliovirus and the mixture assayed for virus by the plaque test.

Major Findings: The poliovirus inhibitor is unlike antibody, does not irreversibly inactivate virus and does not inhibit some Coxsackie and ECHO viruses. The inhibitor is sedimented by centrifugation at 1000 RPM for 30 minutes.

Significance to the Division. Will provide information to determine methods for elimination of inhibitor which interferes with poliovirus isolation. Also will provide information relative to importance of inhibitor in pathogenesis of poliovirus infection of the nervous system.

Proposed Course: Determination of (1) chemical treatment which will inactivate inhibitor (2) mechanisms of action of inhibitor and (3) effect of inhibitor on experimental poliovirus infections of animals.

Sub-project E: Correlation of Antibody Response to Poliomyelitis Vaccine in Man, Monkey and Chick.

Objective: To provide information so that animal potency requirements for polio vaccine may be established at a level which will provide a desired response in man.

Methods Employed: Varying amounts of poliovirus vaccine antigen were administered to children and their serums assayed for poliovirus antibodies at suitable intervals. Animal potency tests were performed on the same vaccines.

Patient Material: In cooperation with the District of Columbia Department of Health, a group of non-vaccinated children were recruited for the study.

Major Findings: Data are being analyzed.

Significance to the Division: Improvement of potency standards for poliomyelitis vaccine.

Proposed Course: Analysis of data and proposal of suitable animal potency requirements.

Sub-project F: Development of a Semi-automatic Diluting Machine.

Objective: To develop a machine which will perform most of the time-consuming dilutions which are required in an immunology laboratory.

Methods Employed: A design of such a machine was discussed with the instrument shop at NIH. Following completion of the machine tests were performed to evaluate its performance.

Major Findings: The machine was found capable of accurately diluting antibody, hemagglutination or dye simultaneously in 12 parallel operations. A major time saving was observed.

Significance to the Division: A machine is now in use which saves a great deal of time and money and which enhances the accuracy of diluting operations.

Proposed Course: Description of the machine in a paper to be published in the scientific literature. Paper has been submitted for publication.

Sub-project G: Investigation of Vacuolating Agent in Live Poliovirus Vaccines.

Objective: To determine whether vacuolating agent is present in vaccines which have been employed and whether there has been any immunologic response in people receiving this agent.

Methods: American and Russian Sabin Vaccine preparations, together with Lederle and Koprowski vaccines have been assayed for vacuolating agent activity. Serum samples from adults receiving vacuolating agent in vaccines have been assayed for development of antibody to the agent. Finally, stools of vaccinees have been assayed for the agent.

Major Findings - All vaccines tested so far have been found to contain 1-3 Log_{10} of vacuolating agent. People receiving the vaccine containing vacuolating agent neither developed antibody nor excreted virus.

Significance to the Division: The vacuolating agent is a possible contaminent of any live vaccine prepared in monkey kidney. Investigation of its properties is most imperative.

Proposed Course: Further investigation of the properties of the vacuolating agent.

Part B included Yes/ X / No/ /

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications:

1. Kirschstein, R., Borman, G., Baron, S., Friedman, R., Murray, R., Hottle, G., Laboratory Investigations of the Attenuated Poliovirus Vaccine Strains. I. Neurovirulence after Intramuscular Innoculation of Monkeys in Live Poliovirus vaccines. Second Intl. Conf. Live Poliovirus Vaccines. Scientific Publications, No. 50, Pg.90, 1960

2. Baron, S., Friedman, R.M., Kirschstein, R.L., Borman, G. L., Murray, R., and Hottle, G.A., Laboratory Investigations of the Attenuated Poliovirus Vaccine Strains. II. Tissue Culture Characteristics before and after Gastrointestinal Passage. Ibid. Pg. 124, 1960

3. Low, R., and Baron, S., Poliovirus Inhibitor from the CNS of the Rhesus Monkey, Science; 132: 622-623, 1960

Serial No. DBS 17
1. Viral Immunology
2. Tissue Culture Unit
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Monkey Safety Test for Poliomyelitis Vaccine and Adenovirus Vaccine.

Principal Investigator: Ruth L. Kirschstein, M.D.

Other Investigators: Dr. Gerald S. Borman, Dr. Gerald L. Van Hoosier.

Cooperating Units: Serology Unit screens monkey serums for freedom from antibody to poliovirus.

Man Years:
Total: 12.0
Professional: 1.0
Other: 11.0

Project Description:

Objectives:

To test poliomyelitis and adenovirus vaccine for the presence of residual active virus particles which can be detected by the direct inoculation of monkeys.

Methods Employed:

As outlined by the PHS regulations for the above vaccines.

Major Findings:

During 1960, 32 of 125 poliomyelitis vaccines and 8 of 27 adenovirus vaccines were tested for safety in monkeys. Nine-hundred-twenty monkeys were examined. Histologic lesions were found in 8 monkeys. These were not lesions of poliomyelitis and from one of the 8 monkeys, Virus B (of Sabin) was recovered from the central nervous system tissues.

Significance to the Program of DBS: Integral part of the DBS program.

Proposed Course: This endeavor will continue in 1961 on the same scale.

Part B included Yes / X / No/ /

Part B. Honors, Awards, and Publications

Kirschstein, R. L., Van Hoosier, G. L., and Li, C. P., Virus-B Infection of the Central Nervous System of Monkeys Used for the Poliomyelitis Vaccine Safety Test, American Journal of Pathology (in press).

Serial No. DBS 18
1. Viral Immunology
2. Tissue Culture Unit
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: The tissue culture preparation and tissue culture testing of killed virus vaccines.

Principal Investigator: Dr. Paul Gerber

Other Investigator: Mr. Robert Grubbs

Cooperating Units: Monkey and rabbit tissues provided by the monkey safety testing unit.

Man Years:

Total: 6.5
Professional: 0.5
Other : 6.0

Project Description:

Objectives: To prepare primary and continuous cell cultures for research and test purposes and to test vaccines for safety by tissue culture methods.

Methods Employed: Testing methods follow those outlined in the Regulations and tissue culture methods are similar to those reported in the scientific literature.

Major Findings: (1) During this year samples of 54 polio vaccines (7 manufacturers) and of 14 Adeno vaccines (3 manufacturers) were tested for safety in tissue culture. (2) From December 1, 1959 to November 30, 1960 the following cell cultures were prepared:

(a) Primary Cell Cultures. See attached
(b) Stable Cell Cultures. See attached

Date_____

Annual
Primary Culture Production

Annual Report for: January 1, 1960 - December 31, 1960

Culture Productions:

Type of Culture	Tubes	Bottles 2 oz.	Bottles MDB*	Bottles 32 oz.
Monkey Kidney - Rhesus	82,753	59,763	8,286	4,447
Monkey Kidney - Grivet	10,932	168	54	36
Monkey Kidney - Vervet	6,695	142	94	66
Monkey Kidney - Patas	400	144	--	10
Monkey Kidney - Marmoset	229	--	--	--
Monkey Testes - Rhesus	550	--	--	--
Monkey Testes - Patas	600	10	--	--
Monkey Ovary - Grivet	48	--	--	--
Monkey Ovary - Vervet	50	--	--	--
Rabbit Kidney	4,600	10,050	60	148
Guinea Pig Kidney	1,150	245	--	20
Cat Kidney	--	52	47	--
Dog Kidney	--	50	--	--
Rabbit Testes	10	--	2	--
Mouse Embryo	--	--	--	6
Rat Embryo	370	415	711	166

* MDB =- Milk Dilution Bottles

No. & Type Tissues Processed	Vol. Packed Cells	Prepared for Serology
Monkey Kidney Rhesus-1,903	5,049 cc	44,765 ml cell suspension
Monkey Kidney-Grivet- 44	58 cc	
Monkey Kidney-Vervet- 20	45 cc	
Monkey Kidney-Patas - 2	6 cc	230 ml of packed Rhesus
Monkey Kidney-Marmoset- 8	2 cc	monkey kidney cells were
Monkey Testes -Rhesus- 18	2.2 cc	given to various in-
Monkey Testes -Patas- 2	1.5 cc	vestigators of NIAID and
Monkey Ovary -Grivet- 2	0.2 cc	NCI.
Monkey Ovary -Vervet- 2	0.2 cc	
Rabbit Kidney - 476	421 cc	
Guinea Pig Kidney - 56	23 cc	
Cat Kidney - 3	6.5 cc	
Dog Kidney - 2	7 cc	
Rabbit Testes - 4	0.1 cc	
Mouse Embryo - 6	2 cc	
Rat Embryo - 709		

Annual Report for December 1, 1959 - November 30, 1960.

Type of Culture	Tubes	2 oz.	MDB	32 oz.
HEP II	6,215	1,386	780	405
Human Amnion	9,016	1,146	22	247
HeLa	8,195	1,056	24	257
Monkey Stable	825	892	36	1
Chang's Liver	400	102	21	--
L-Cells	75	170	--	10
KB	545	220	12	--

Serial No. DBS 19
1. Viral Immunology
2. Section on Testing, Serology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: The Measurement of Antipoliovirus Antibodies by the Metabolic Inhibition Test (MIT).

Principal Investigator: Dr. B. Wm. Uhlendorf

Other Investigators: Mrs. Beatrice Burch

Cooperating Units: The Tissue Culture Unit supplies suspensions of monkey kidney cells.

Man Years:

Total: 2.2
Professional: 0.4
Other: 1.8

Project Description:

Objectives: 1. To screen for the presence of anti-poliovirus antibodies in pre-vaccination sera of monkeys used for the monkey potency-test, in sera from monkeys used for the safety test, and in sera from chicks used for the chick potency test. To determine the relative antibody content of post-vaccination sera from potency test monkeys. To determine the anti-poliovirus antibody titer of human sera collected in field studies, and of commercial gamma-globulin preparations for standardization purposes.

2. To examine the effect of variation of technique and reagents used for the MIT on the reliability of the test.

Methods: 1. During the year approximately 1196 sera of all kinds were titered for antibody content, against the three types of poliovirus, and 10,665 sera screened.

2. By defining and approximately adjusting the reagents and techniques it has been possible to improve to a considerable extent the reliability of the MIT.

Significance to the Program of DBS: Integral part of DBS testing program.

Part B included.

Serial No. DBS 20
1. Viral Immunology
2. Section on Testing, Serology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

PART A

Project Title: The Antigenic Potency of Poliomyelitis Vaccine as Determined in Chicks and in Monkeys.

Principal Investigator: Dr. B. Wm. Uhlendorf

Other Investigators: G. L. Van Hoosier, D.V.M.

Cooperating Units: None

Man Years:

Total: 6.2
Professional: 0.2
Other: 6.0

Sub-project A:

Project Description:

Objectives: 1. To determine the antigenic potency of poliomyelitis vaccine. 2. To determine the relative merits of the chick test and the monkey test for determining the antigenic potency of poliomyelitis vaccines.

Methods: The methods are those outlined in the PHS Regulations and in the scientific literature.

Major Findings: 1. During the year, 45 vaccines were tested by the monkey test involving 528 monkeys. 2. During the year, 101 vaccines (including reference vaccines) were tested by the chick test involving the use of approximately 8000 chicks. 3. The chick test appears to be a satisfactory test for determining the antigenicity of poliomyelitis vaccine and in many respects it may be more valid than is the monkey test.

Significance to the Division: This is part of the DBS Poliomyelitis Vaccine Testing program. The comparison of the chick test is necessary to establish minimum potency requirements in the probable event that the chick test will officially replace the monkey test for the method of determining antigenicity of poliomyelitis vaccine.

Sub-project B:

During the year the laboratory participated in an international cooperative project conducted by WHO. In this project, a number of reference vaccines were tested by the monkey test and chick tests of two different designs. The purpose of the project was to provide data for the selection of an international reference poliomyelitis vaccine.

Serial No. DBS 21
1. Viral Immunology
2. Test Development Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Study of Immunity to Poliovirus and Other Virus Infections. Study of Immune Mechanism.

Principal Investigator: Dr. Samuel Baron

Other Investigators: Dr. Robert Friedman
Dr. G. Economos, Medical Director
D. C. Children's Center, Laurel, Maryland
Dr. Sam Silbergeld, DRG
Dr. James E. Boyland, D. C. Children's Center, Laurel, Maryland
Dr. John P. Nasou, NIAID
Dr. George M. Owen, NIAID
Dr. B. W. Uhlendorf
Dr. A. Holtz

Man Years
Total: 2-1/2
Professional - 1/2
Other: 2

Sub-project A: Rapid Immunization with Poliomyelitis and Mumps Vaccines.

Objective: To determine a dosage schedule of polio vaccine and mumps vaccine which will result in early appearance of immunity and therefore be of value during epidemics of poliomyelitis and prevention of mumps in exposed subjects.

Methods Employed: Various dosage schedules were employed in children and adults and serial bleedings were assayed for neutralizing antibody to poliovirus or mumps.

Patient Material: Children at the Children's Center, and in the District of Columbia, through the D. C. Department of Public Health.

Major Findings: A large single inoculation (10 ml) of average or high potency polio vaccine was capable of evoking antibody within 1 to 2 weeks of inoculation. Results on mumps hyperimmunization are not yet available.

Significance to the Division: Method to provide protection for non-immune persons during a poliomyelitis epidemic. Method to provide rapid immunization in persons exposed to mumps.

Proposed Course: Determination of dosage schedule which will provide rapid immunization, maintain antibody throughout the immunization period and produce high levels of antibody.

Sub-project B: Effect of Administration of Human Gamma Globulin on Infectious Diseases of Children and Aged Persons.

Objective: Determine the ability of gamma globulin to reduce the incidence and severity of certain common infectious diseases.

Methods Employed: This double-blind study in 381 institutionalized elderly adults and 115 children utilized 3 or 6 monthly I.M. inoculations of 0.15 or 0.4 ml. GG per pound. The two populations were each randomly divided into three approximately equal groups, viz. GG, saline placebo, and non-inoculated recipients.

Patient Material: Institutionalized children and elderly adults at D. C. Children's Center and Laguna Honda Home.

Major Findings: Infections among all adults occurred in 3 main categories, totaling 261 episodes and 422 days; among children 7 main categories, totaling 986 episodes and 3588 days. Significant prophylaxis, expressed as % protection based on days (P_d), was observed among children for mumps (P_e,=74, P_d=69), whereas no significant prophylaxis was noted for upper respiratory infections, pneumonia and bronchopneumonia, and fever of unknown origin.

Significance to the Division: This investigation suggests some new limitations and values of GG as a prophylactic agent. Also the information may lead to successful prophylaxis of mumps in man.

Proposed Course: To determine effectiveness of gamma globulin of known antibody content given after exposure to mumps virus. Paper presently being prepared.

Sub-project C: Antibody to Enteroviruses in the Serums of Persons with Hypogammaglobulinemia.

Objectives: To determine whether newly developed, highly sensitive techniques for detection of viral antibody could demonstrate antibody in the serums of persons with hypogammaglobulinemia.

Methods Employed: Immunoinactivation test for virus antibody in serum. Fractionation of serum from Hypogammaglobulinmics on Deae-Cellulose.

Patient Material: Serums from outpatients and inpatients of LID of NIAID.

Major Findings: Detection of extremely low levels of antibody to enterovirus in these serums. The distribution of antibody was normal but diminished in quantity. In one case, two levels of antibody to poliovirus were detected following immunization with polio vaccine. Antibody was present in the gammaglobulin.

Significance to the Division: Information which leads to changed concept of the disease and may explain why these persons are normally resistant to viral infections.

Proposed Course. Write paper on this subject.

Sub-project D: Effect of hypersensitivity, radiation and antimetabolites on immunity to virus infections.

Objectives: To determine whether a state of hypersensitivity to viral antigens is of importance in resistance to virus infection in experimental animals, and to study effect of irradiation and antimetabolites.

Methods Employed: Animals have been made delayed hypersensitive to viral antigens by various methods of immunization. Skin testing and challenge are being carried out on these animals. Immune mechanisms have been blocked by radiation and antimetabolites.

Major Findings: Delayed hypersensitive state has been established to vaccinia following inoculation of live or dead materials. Immune mechanisms are inhibited by a combination of radiation and antimetabolites.

Significance to the Division: Studying a possible mechanism for animal resistance to virus infection.

Proposed Course: Further investigation of the relationship of delayed hypersensitive states to antibody response to viral agents and testing of resistance of hypersensitive animals to virus infections. Establishment of whether delayed hypersensitivity is a necessary precursor to antibody production against viral antigens and establishing what, if any, resistance is conferred upon animals which are made delayed hypersensitive in the

absence of antibodies. Two papers are being prepared on this subject.

Sub-project E. Distribution of antibody in Serum Proteins During Immunization and Diseases Affecting Gamma Globulin.

Objectives: To fractionate serum in order to locate and identify antibodies in the various fractions of sera obtained from patients in unusual immunologic states.

Methods Employed: Cellulose resin columns - DEAE and CM to fractionate serum and immunoinactivation for evaluation of serum antibody content.

Patient Materials: Sera from volunteers from Employee Health Service, NIH, who received 10 cc. of polio vaccine and hypogammaglobulinemic patients of the NIAID.

Major Findings: Methods have been applied by which serum may easily be divided into various pure fractions in our laboratory.

Significance to the Division: Better understanding of what factors in serum are responsible for resistance to virus infection and of immune process in general.

Proposed Course of Project: Fractionation of EHS and hypogammaglobulinemic sera together with any sera we can obtain from patients with disorders in the RE system, i.e., lymphomas, leukemias, myeloma, cirrhosis, etc.

Sub-project F. Relationship between interferon and recovery from virus infections.

Objectives: To determine whether interferon is important in recovery of Guinea pigs during the course of their infection with various agents.

Methods Employed: Guinea pigs are infected with vaccinia and the infection site assayed for interferon. Also, interferon produced in Guinea pig kidney is assayed for protective effect in Guinea pigs and rabbits.

Major findings: First experiments were just initiated at the time of this report.

Significancd to the Division: Studying a possible mechanism for resistance of animals to virus infection.

Proposed Course: Development of accurate methods for assay of interferon in a Guinea pig system and investigation of the possible production of interferon in Guinea pigs during virus infections.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications:

Barnett, E.V., Nasou, J.P., Utz, J.P. and Baron, S. Antibodies to Enteroviruses in Hypogammaglobulenemic Patients. New Eng. Jour. Med., 262; 563-565, 1960

Serial No. DBS 22
1. Viral Immunology
2. Section on Testing
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Experimental Studies with Viruses and Cell Cultures.

Principal Investigator: Dr. Samuel Baron

Other Investigators: Dr. C. W. Hiatt
Dr. R. Friedman

Man Years:

Total 1
Professional 1/2
Other 1/2

Sub-project A: Comparative Study of Ultraviolet Light Inactivation of Animal Viruses.

Objectives: Determination of the ultraviolet light inactivation properties of a number of animal viruses for characterization and classification.

Methods employed: Aqueous suspensions of various viruses are exposed to ultraviolet radiation. Samples are taken at appropriate intervals and assayed for infectivity. Plots are then made for each virus relating decline of infectivity with time of irradiation. Intensity of irradiation is measured with an Archer radiation meter and also by inactivation of a standard virus preparation (poliovirus Type III, Saukett strain).

Major Findings: Inactivation rate and slope are correlated with relationship of viruses as determined by other properties. Inactivation rate is not proportionate to virus size as is true of bacteriophage.

Significance to the Division: Basic information on the physical property of ultraviolet light inactivation of viruses. Potential application for identification and classification of viruses.

Proposed Course: Write paper for publication.

Sub-project B: Plaque Size Inhibition as an Assay of Antibody and Inhibitor to Poliovirus.

Objectives: Development of a new and easier technique for the assay of poliovirus antibody by the use of a method which does not require serial dilution of serum.

Methods Employed: Monolayers of monkey kidney cell culture are infected with small amounts of poliovirus and then overlayed with agar containing immune serum. Diameters of resulting plaques are measured in comparison to serum-free control plaques. Results are analyzed for correlation with known serum antibody titer, reproducibility and variation among sera from different species.

Major Findings: Plaque size inhibition is well correlated with poliovirus antibody titers as measured by accepted tests. Reproducibility appears somewhat better than the metabolic inhibition test. Antiserum from man, chicken, and monkey are indistinguishable by the plaque size inhibition test. In tests of over 300 sera, methods have been developed for rapid large scale application.

Significance to the Division: Potential application in the serology unit for potency tests of poliomyelitis vaccine in animals and man. Theoretical implications relating to pathogenesis of poliomyelitis.

Proposed Course of Project: Write paper for publication.

Sub-project C: Antigenic Crossing of the 3 types of poliovirus.

Objectives: To determine the antigenic relationship among the 3 types of poliovirus.

Methods Employed: Serums from rabbits immunized with plaque-purified poliovirus assayed for antibody by extremely sensitive techniques (Immunoinactivation).

Major Findings: Rabbits immunized to a single poliovirus (Type 1) respond with high levels of antibody to the homotypic virus and with extremely low levels of antibody to 1 or 2 heterotypic viruses.

Significance to the Division: Basic information on the sharing of common antigens by polioviruses.

Proposed Course: Paper submitted for publication

Sub-project D: Viral Sensitivity of Cell Culture Maintained in Skim Milk Medium.

Objectives: To determine suitability of skim milk medium for viral assays in cell cultures.

Methods Employed: Comparative assay of 22 viruses in cell cultures maintained with skim milk medium and with an established maintenance medium.

Major Findings: All viruses, except adenoviruses manifest full titer in cell cultures maintained with skim milk medium. Due to a cell-mediated effect adenovirus titers are one $\log_{10}$ lower in skim milk medium than in Ginsberg's medium.

Significance to the Division: Sub-project completed.

Serial No. DBS 23
1. Viral Immunology
2. Tissue Culture Unit
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Studies of the Neurovirulence of the Attenuated Polioviruses (live vaccine) Strains in Monkeys.

Principal Investigator: Ruth L. Kirschstein

Other Investigators: Dr. Samuel Baron, Dr. Robert Friedman
Dr. Gerald Borman, Dr. Gerald Van Hoosier,
Mr. George Rusten.

Cooperating Units: None

Man Years:

Total: 2.5
Professional: 1.5
Other: 1.0

Project Description:

Objective: To further study the neurovirulence of the nine strains of attenuated polioviruses that have been used in field trials and of the viruses excreted after feeding to man.

Methods: Inoculation of these strains by an intramuscular route using varying titers of the viruses was performed. Approximately 400 monkeys were used in this study. Careful histopathologic study of the spinal cord and brain tissue was carried out. Attempts to infect monkeys orally were also made.

Major Findings: Some strains of attenuated polioviruses are capable of inducing paralysis in monkeys after intramuscular inoculation of titers of $10^{7.7}$ PFU/ml. or greater. Other strains produce restricted histologic lesions of CNS but no paralysis.

Significance to the Program of DBS: This study has provided an important basis for the criteria of acceptability of candidate strains for live poliovirus vaccine.

Proposed Course: Safety testing of vaccines submitted by manufacturer will be carried out according to the regulations that have been written. In addition, continued studies as to the pathogenesis of poliomyelitis and the relationship of monkey neurovirulence and human neurovirulence are underway.

Part B included Yes/ X / No/ /

Part B Honors, Awards and Publications.

1. Kirschstein, R. L., Baron, S., Borman, G., Murray, R., Perkins, F. T., and Hottle, G., Neurovirulence of Attenuated type I Poliovirus Vaccine Strains after intramuscular Inoculation of Rhesus Monkeys. Virology 11:300 (1960)

2. Kirschstein, R. L., Borman, G., Baron, S., Friedman, R., Murray, R., and Hottle, G. Laboratory Investigations of the Attenuated Poliovirus Vaccine Strains: I. Neurovirulence after Intramuscular Inoculation of Monkeys. Second International Conference on Live Poliovirus Vaccines, Scientific Publication No. 50, Pan American Health Organization, 1960, pages 90-97.

3. Baron, S., Friedman, R., Kirschstein, R., Borman, G. Murray, R., and Hottle, G. Laboratory Investigations of The Attenuated Poliovirus Vaccine Strains: II Tissue Culture Characteristics Before and After Gastrointestinal Passage. Ibid: pages 124-131

Serial No. DBS 24
1. Viral Immunology
2. Tissue Culture Unit
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Pathogenesis of Infectious Diseases

Principal Investigator: Ruth L. Kirschstein

Other Investigators: Dr. Alan Rabson, NCI
Dr. Bernice Eddy
Dr. Gerald Van Hoosier
Dr. Gerald Borman
Dr. Robert Friedman
Dr. Harold Baer

Cooperating Units: Laboratory of Bacterial Products
Laboratory of Virology and Rickettsiology
Pathologic Anatomy Branch, NCI

Man Hours:

Total: 1.0
Professional: 0.5
Other: 0.5

Project Description:

Objective: To study the pathogenesis of various experimental infectious diseases.

Methods: Gross autopsies and histologic examinations were carried out on infected animals.

Major Findings:

1 -(With Dr. Rabson). The pathology of the intracranial sarcomas produced in hamsters by the polyoma virus has been studied in detail. The early changes and the pathogenesis of these lesions are being studied in detail at the present time.

2 - (With Drs. Eddy and Borman). Tumors produced by polyoma virus have been studied and are considered undifferentiated sarcomas.

3 -(With Drs. Van Hoosier and Borman). Studies of the pathogenesis of lesions produced by a fibromalike virus of monkeys in newborn monkeys are in progress.

4 -(With Drs. Van Hoosier and Borman). Studies of the neurovirulence of various enteric viruses are in progress.

5 - (With Drs. Friedman and Baer). Studies of the histologic changes induced by delayed hypersensitivity, immediate sensitivity and complete and incomplete Freund's adjuvant are in progress.

6 - (Drs. Borman and Eddy). Tumors induced in newborn hamsters by inoculation of frozen and thawed monkey kidney cell cultures were studied and considered to be undifferentiated sarcomas that differed slightly from those induced by polyoma virus.

7.- (Drs. Borman, Li and Holtz). The pathogenesis of polyoma virus - induced hydrocephalus in Swiss mice is under study.

8. -(Drs. Borman and Gerber). Viral induced morphological alteration of cell culture systems are to be examined. Preliminary characterization of uninoculated cell cultures of various species is in progress.

9. -(With Drs. Borman and Seligman). Testing of a secondary seed lot of "17-D_ Yellow Fever vaccine intracerebrally in monkeys has been carried. The vaccine met the U.S.P.H.S. Regulations and the W.H.O. recommendations as to monkey neurovirulence.

Part B. included Yes /X/ /___/

Part B Honors, Awards and Publications.

1. Gerber, P., and Kirschstein, R. L.
Biological Properties of Ribonucleic Acid from Virulent and Attenuated Poliovirus, J. of Exp. Med. 111:525 (1960)

2. Rabson, A.S., and Kirschstein, R.L.
Intracranial Sarcomas produced by Polyoma virus in Syrian hamsters, Arch. of Path.

3. Eddy, B.E., Borman, G., Kirschstein, R.L., and Touchette, R. H., Neoplasma in Guinea Pigs infected with S. E. Polyoma Virus, Journal of Infectious Diseases (in press).

4. Borman, G.S., Olson, C., and Segre, D. The Trigeminal and Facial Nerves as Pathways for Infection of Sheep with Listeria monocytogenes, Am. J. of Vet. Research 21:993 (1960) [Work completed prior to joining the staff of NIH].

Serial No. DBS 25
1. Viral Immunology
2. Tissue Culture Unit
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Experimental Studies with Cell Cultures.

Principal Investigator: Dr. Paul Gerber

Other Investigator: None

Cooperating Units: None

Man Years

Total: 0.3
Professional: 0.1
Other: 0.2

Sub-project A: Maintenance of a frozen tissue cell bank.

Objectives: Long term frozen storage of continuous cell lines for use in cell culture work.

Methods Employed: Sample strains of continuous cell lines derived from human monkey and rabbit tissues are frozen under controlled conditions in the presence of critical concentrations (5-20%) of glycerol. The sealed ampules are stored at -60° to -70°C.

Major Findings: All of the 10 cell lines stored in the frozen state retained viability for at least 24 months.

Significance: Availability of a frozen cell culture collection eliminates the time consuming task of maintaining stock cultures and the inherent risk of contamination by other cell lines or by micro-organisms, and minimizes the emergence of genetic variants.

Proposed course. This is a continuing project.

Sub-project B: Studies on latent infections of continuous cell lines with PPLO.

Objectives: Elimination of these micro-organisms from cell cultures.

Methods Employed: Hep II cells which are heavily injected with PPLO were grown and subcultured weekly for 10 weeks at 40°C with the intent to inactivate the micro-organisms.

Major Findings: This treatment failed to eliminate the infection.

Significance: Efforts will continue to find a suitable method of eliminating PPLO or bacterial L-forms from continuous cell cultures.

Serial No. DBS 26
1. Viral Immunology
2. Section on Testing
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

PART A

Project Title: Biological Properties of Ribonucleic acid from Virulent and Attenuated Poliovirus.

Principal Investigator: Dr. Paul Gerber

Other Investigator: Dr. Ruth L. Kirschstein

Cooperating Units: None

Man Years:

Total: 0.5
Professional: 0.3
Other: 0.2

Project Description:

Objectives: Study relationship of neurovirulence of type I poliovirus to viral RNA.

Methods employed: Infective RNA obtained from virulent and attenuated polioviruses was injected intraspinally into mice and also tested for in vitro markers of neurovirulence.

Major findings: Results suggest that infective RNA from type I poliovirus carries the genetic information which determines the degree of neurovirulence.

Significance: Basic information on virus-host all interaction.

Proposed course: This phase of the study is completed, and the results were published.

PART B Honors, Awards and Publications

Paul Gerber and Ruth Kirschstein. Biological Properties of Ribonucleic Acid from Virulent and Attenuated Poliovirus.

Journal of Experimental Medicine
Volume III 525-532 1960

Serial No. DBS 27
1. Viral Immunology
2. Section on Testing
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Studies on the Vacuolating Agent

Principal Investigator: Dr. Paul Gerber

Other Investigators: Dr. Caspar Hiatt
Dr. Robert M. Friedman

Cooperating Units: None

Man Years:
Total: 0.2
Professional: 0.1
Other: 0.1

Sub-project A: Selective inactivation by photodynamic action of agent in experimental lots of attenuated poliovirus.

Objectives: Elimination of adventitious agents, such as the vacuolating agent, from seed lots of attenuated poliovirus.

Methods Employed: Mixtures of vacuolating agent and attenuated poliovirus of known titers are exposed to the photodynamic effect of light for various time intervals. Samples are assayed for residual viral content.

Major Findings: The Vacuolating agent is highly sensitive to photodynamic inactivation whereas poliovirus is resistant.

Significance to Division: Elimination of contaminating simian viruses of unknown potential pathogenicity for man in live virus vaccines is desirable.

Proposed course: Complete the present study and prepare a manuscript for publication.

Sub-project B: Search for residual vacuolating agent in commercial lots of Salk type polio vaccine.

Objectives: To determine if the vacuolating agent is present in killed polio vaccine. Compare formalin inactivation curve vacuolating agent and poliovirus.

Methods employed: Methods follow closely the procedure used in the tissue culture safety tests for polio vaccine using Vervet kidney cells in place of Rhesus kidney cells. The formalin inactivation studies are similar to work published in the literature.

Major findings: This project has just begun.

Significance: Detection of residual vacuolating agent in killed polio vaccine may require changes in the Regulations regarding procedures for formalin inactivation.

Proposed course: Several randomly selected samples of commercial lots of polio vaccine are being tested.

Serial No. DBS 28
1. Viral Immunology
2. Animal Testing Unit
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Investigation of Antigenic Variation and the Neutralization of Herpes virus.

Principal Investigator: G. L. Van Hoosier, Jr., D.V.M.

Cooperating Units: Viral and Rickettsial Disease Laboratory, California State Department Public Health, Berkeley, California.

Man Years:
Total: 0.6
Professional: 0.3
Other: 0.3

Project Description:

Objective: To study the variable factors involved in the neutralization of herpes virus in an effort to develop a highly sensitive test for antibody; to compare strains of herpes virus of various origins in the sensitive neutralization test.

Major Findings: Conventional neutralization and complement fixation tests were not sensitive enough to distinguish between strains of human and animal origin.

Proposed Course: Project to be continued.

Serial No. DBS 29
1. Viral Immunology
2. Animal Testing Unit
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960.

Part A

Project Title: Serological characterization of some 1960 strains of Swine Influenza Virus.

Principal Investigator: G. L. Van Hoosier, Jr. D.V.M.

Cooperating Units: Viral and Rickettsial Disease Laboratory, California State Department Public Health, Berkeley, California.

Man Years:
Total: 0.3
Professional: 0.3

Project Description:

Objective: To determine if 1960 strains of swine influenza virus were of the swine or human type.

Major Findings: 1960 strains were related to the prototype swine strain (A/Swine/31); no evidence of swine infection with the A2 (Asian) or other human strains was obtained.

Proposed Course: Project terminated.

97

Serial No. DBS 30
1. Viral Immunology
2. Section on Testing, Serology.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Application of the MIT for titrations of viruses other than poliovirus.

Principal Investigator: Dr. B. Wm. Uhlendorf

Other Investigators: Dr. R. Friedman

Cooperating Units: The tissue culture unit supplies suspensions of monkey kidney cells.

Man Years:

Total: 0.2
Professional: 0.1
Other: 0.1

Project Description:

1. Objectives: To develop techniques by which cells, other than monkey kidney cells, can be used for in the MIT.

2. To develop techniques for the titration of other viruses than poliovirus.

3. To develop techniques for the measurement of antibodies against other viruses.

4. To develop techniques for the measurement of anti-viral substances.

Major Findings: Of systems tried so far vaccinia and an influenza guinea pig cell system seem promising.

Significance to the Division: Would give the Division a simple method for assay of viruses important in the regulation of vaccines.

Proposed course: Confirm present findings and extend the system to other viruses.

Serial No. DBS 31
1. Viral Immunology
2. Section on Testing, Serology
3. Bethesda, Maryland.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Development of new electronically controlled Automatic Diluting Machine

Principal Investigator: Dr. B. Wm. Uhlendorf

Other Investigators: None

Cooperating Units: None

Man Years:

Total: 0.4
Professional: 0.3
Other: 0.1

Project Description:

Objectives: To further develop this machine and obtain data for its application to varied serologic techniques such as metabolic inhibition, hemagglutination titrations, hemagglutination-inhibition titrations and compliment-fixation titrations, and also to develop techniques for the use of this machine for these tests on a semi-micro scale.

Major Findings: 1. The machine is well suited for the applications stated above; it is more precise and much faster than standard techniques. 2. For semi-micro work, which has application where limited volumes of sera must be tested for antibodies against a large number of antigens, a new type of plastic cup-plate must be used. Specifications have been drawn up for such a plate. 3. At least one manufacturer is planning to produce the machine for the use of general scientific public.

Serial No. DBS 32
1. Laboratory of Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: General Aspects of Virology & Rickettsiology

Principal Investigator: Dr. Joseph E. Smadel

Other Investigators: Elizabeth B. Jackson

Cooperating Units: U. S. Naval Medical Research Unit, Taipei, Taiwan

Man Years: (Calendar Year 1960)

Total: 1/2
Professional: 1/2
Other: None

Objectives: This particular project is included among those of the Laboratory of Virology and Rickettsiology in order to provide a mechanism for reporting work which does not fall clearly within the purview of other Project Reports. The principal laboratory research presented this year is concerned with antigenic studies of trachoma virus. The remainder of the report lists several publications in the general field of immunology, virology and rickettsiology.

Methods Employed: Standard procedures used in a research laboratory for the study of viral and rickettsial agents were employed.

Major Findings: One of the members of this laboratory participated, as a guest scientist at the U. S. Naval Medical Research Unit No. 2, Taipei, Taiwan, in a study on the serological relationship of trachoma, psittacosis and lymphogranuloma viruses. The results of this work were published, (See reference cited in Part B.) As had been reported by earlier workers, it was found that persons infected with trachoma, psittacosis or lymphogranuloma venereum viruses developed antibodies which reacted in complement fixation tests with psittacosis-lymphogranuloma group antigens prepared from yolk sacs infected with any one of these agents. Purified washed elementary body antigens prepared from each of the three viruses clearly differentiated sera of patients with trachoma from sera of patients with psittacosis or lymphogranuloma venereum. However, these antigens failed to differentiate between the two latter infections.

DBS Serial No._____

Significance to Bio-medical Research and the Program of the Division: Constant review of immunization procedures for viral and rickettsial diseases from the point of view of informing the physician of the value of current vaccines is a contribution which this laboratory can make to preventive medicine.

Unforeseen problems of an acute nature arise in this field from time to time. These may be solved in a relatively short interval by intense study. Therefore, it is important to maintain a nucleus of experienced workers well grounded in basic virological techniques who can be deployed at short notice to assist in such contingencies.

Proposed course of Project: Work will be continued along the lines described.

Part B. Included Yes X No_____

Part B.

Honors, Awards and Publications

Publications other than abstracts from this project:

1. Woolridge, R. L., Jackson, E. B., and Grayston, J. T. Serological relationship of trachoma, psittacosis and lymphogranuloma venereum viruses. Proc. Soc. Exper. Biol. and Med. 104: 298-301, 1960.

2. Smadel, J. E. Tumor virus research program. In Symposium:phenomena of tumor viruses, National Cancer Institute Monograph No. 4. U. S. Dept. Health, Educ., and Welfare, P. H. S. 1960.

3. Smadel, J. E. Immunization for young and old. Maryland State Med. J. 9: 538-546, 1960.

4. Smadel, J. E. Rocky Mountain spotted fever vaccine. To be published in Symposium on Rocky Mountain Spotted Fever. Med. Sci. Pub. No.____. Walter Reed Army Institute of Research. (in press).

Serial No. DBS 33
1. Laboratory of Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Growth and Metabolism of Rickettsiae

Principal Investigator: Hope E. Hopps

Other Investigators: J. E. Smadel, J. L. Showacre, B. C. Bernheim

Cooperating Units: Cytology and Metabolism Unit, LBV, NIAID

Man Years: (calendar year 1960)
Total: 2 2/3
Professional: 1 2/3
Other: 1

Project Description:

Objectives: The main objective is the accumulation of information which may lead to eradication of the carrier state in persons convalescent from typhus and typhoid fevers through studies on tissue cultures infected with rickettsiae or Salmonella typhosa and subjected to various experimental procedures.

Methods Employed: The ordinary procedures used in a research laboratory engaged in studies on rickettsial and other microbial agents were employed.

Major Findings: Carrier state in typhoid fever. The carrier state and mechanisms of survival of antibiotic treated intracellular organisms have been studied extensively in this laboratory through the use of tissue culture systems infected with either rickettsiae or with Salmonella typhosa. Studies with the latter organism have been brought to completion in the past year and are summarized in this report.

It has been demonstrated for the first time, by direct observations employing phase microscopy that several antibiotics (chloramphenicol, penicillin, streptomycin and synnematin B) penetrate mammalian cells rapidly and promptly inhibit division of intracellular S. typhosa; however, this process is not followed by rapid death and disappearance

of the intracellular organisms. In a total of 70 experiments, S. typhosa was eradicated in 22 instances but only after prolonged therapy (usually 3 weeks); the most effective antibiotic in this regard was synnematin B which was responsible for 20 of the 22 cures.

Detailed quantitative experiments with this antibiotic revealed a characteristic pattern in death of viable organisms in the drug treated tissue cultures, viz., approximately 99% of the organisms were dead after 48 hrs exposure to synnematin but the remaining 1% (approximately 10^3-10^4/ml) persisted for several weeks. Comparisons of synnematin action on cultures of S. typhosa growing in ordinary nutrient broth or in acellular tissue culture medium in either the logarithmic or stationary growth phase revealed that the actively growing bacilli were rapidly killed while the stationary phase organisms in complex medium survived for 2 weeks or more. In some respects the persistence of S. typhosa in treated tissue culture cells appears similar to that of stationary phase organisms in the presence of antibiotic. This suggests that: (1) the microbial population introduced into the tissue culture may contain a small proportion of non-multiplying and, hence, antibiotic refractory bacilli; or (2) the inocula used for the tissue cultures may consist entirely of actively multiplying organisms but some of the antibiotic damaged bacilli assume certain characteristics of the stationary phase organism, at least with regard to antibiotic response. In any case, death of the persisting intracellular bacteria may possible result from inanition in the presence of the test antibiotic in contrast to some other mechanism by which the antibiotic may cause death of the actively growing bacterium in broth.

Significance of the Program to the Institute. The carrier state and the resistance of intracellular microbes to antibiotics are among the more important problems facing those interested in the control of infectious diseases.

Proposed course of the project. Experimental work concerning intracellular S. typhosa having been brought to a close, studies to examine the mechanism by which tissue cells are freed of microbial invaders will be initiated from another approach. Earlier investigation showed that viability of intracellular rickettsiae in tissue cultures was markedly influenced by the nutritional state of the host cells, i.e., when the infected cells were suspended in non-nutritive media, loss of rickettsial infectivity occurred at approximately the same rate as when actively multiplying infected tissue cells were treated with moderate amounts of antibiotic. Experiments concerning the possible role of antibody formation in vitro in host cells infected with rickettsiae will be undertaken to determine whether such a process is important in the clearing mechanisms which in nature lead to recovery of the cell and the host.

Part B. included: Yes x No____

Serial No. 33

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Smadel, J. E., Some aspects of intracellular infections. J. Immunol. 84: 1-5, 1960. (Listed in 1959 report as in press.)

Showacre, J. L., Hopps, H. E., duBuy, H. G. and Smadel, J. E. Effect of antibiotics on intracellular Salmonella typhosa. I. Demonstration by phase microscopy of prompt inhibition of intracellular multiplication. J. Immunol.(In press)

Hopps, H. E., Smadel, J. E., Bernheim, B. C., Danauskas, J. X. and Jackson, E. B. Effect of antibiotics on intracellular Salmonella typhosa. II. Elimination of infection by prolonged treatment. J. Immunol. In press.

Serial No. DBS 34
1. Laboratory of Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Typhus vaccine - living attenuated Strain E

Principal Investigator: Elizabeth B. Jackson

Other Investigators: Dr. J. A. Morris, C. G. Aulisio, S. Berman

Cooperating Units: Department of Biologics Research, Division of Immunology, WRAIR

Man Years:
Total: 1 1/2
Professional: 1 1/6
Other: 1/3

Project Description:

Objectives: (1) Development of procedures for the production and lyophilization of stable high titer living attenuated epidemic typhus vaccine, Strain E. Development of an acceptable reliable infectivity assay to serve in biologics control. (2) Studies in guinea pigs on the correlation of antibody response with resistance to infection.

Methods Employed: The ordinary procedures used in a research laboratory engaged in studies on rickettsial agents were employed.

Major Findings: (1) Vaccine production and assay. Work by Fox and colleagues has shown that vaccination with 10^4 to 10^5 egg infectious doses (EID) of attenuated Rickettsia prowazeki, Strain E, produced immunity in man sufficient to permit resistance to challenge with virulent rickettsiae. This immunity lasted for at least 5 1/2 years. The need for the development and stockpiling of such a vaccine in the event of a national disaster has been emphasized by the Rickettsial Commission of the Armed Forces Epidemiological Board.

Studies in this laboratory on the behaviour of Strain E rickettsia in the yolk sac of the fertile hens egg, indicate that its growth characteristics in this host do not differ from those of the virulent Breinl strain of R. prowazeki. Thus, some of the same techniques used in the routine production of material for killed epidemic typhus vaccine could be employed in producing living Strain E vaccine, i.e., preparation of standard seed pools, infection of 6-7 day old embryos with a dilution

of seed material which will produce maximal growth of rickettsiae and cause death of 20-30 percent of the embryos on the 7th-8th day after inoculation, harvesting of yolk sacs in pools of 25-35, etc. Crude 50 percent preparations of such heavily infected yolk sacs suspended in sucrose-phosphate-glutamate solution, shell frozen and stored at -70°C have a mouse toxin titer of 1/100-1/200, an egg lethal titer of $10^{-8.0}$ and an egg infectious titer of $10^{-10.0}$. Certain of these materials diluted in several different media and clarified by low speed centrifugation have been lyophilized under varying conditions by the Department of Biologics Research, WRAIR. Tests are being performed to determine the activity of these preparations as measured by their mouse toxin, embryo lethal and embryo infectious titers.

Such data added to that already accumulated on the relationship of embryo lethal titers to embryo infectious titers as determined by observation of yolk sac smears and as determined by blind passage will be useful in defining a reliable infectivity assay for strain E avirulent typhus vaccine.

(2) Studies in guinea pigs on the correlation of antibody response with resistance to infection. Studies were begun in guinea pigs to clarify the relationship between serum antibody levels elicited by injection of varying dilutions of suspensions prepared from yolk sacs infected with strain E of R. prowazeki and resistance to challenge with a fully virulent strain of epidemic typhus rickettsiae (strain Brienl). Subcutaneous injection of 10^9 or 10^{10} egg infectious doses (EID) of strain E induces development of both toxin neutralizing and CF antibodies and an almost solid resistance to challenge with several thousand guinea pig infectious doses of strain Brienl; 10^7 or 10^8 EID elicits CF antibodies and some resistance, but does not induce formation of detectable amounts of toxin neutralzing antibody; while 10^5 or 10^6 EID does not induce levels of either type antibody in guinea pigs, this dose does evoke measurable and significant resistance to challenge. Experiments are in progress to corroborate the relationships in guinea pigs between infectious dose antibody formation and resistance to challenge.

Significance to Biomedical Research and the Program of the Division. Since rickettsiologists and health officers recognize the need for an attenuated vaccine for the control of epidemic typhus in conditions of catastrophe, it behooves the DBS to adquire familiarity with the problem and contribute to the solution of its biologics control aspects.

Proposed Course of the Project: Work will be continued along the lines described above.

Part B. Included Yes_____ No x

Serial No. DBS 35
1. Laboratory of Virology & Rickettsiology
2. General Virology Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Investigations Concerning Measles Virus and Vaccine

Principal Investigator: Dr. Harry M. Meyer, Jr.

Other Investigators: Barbara E. Brooks and Nancy G. Rogers

Cooperating Units: None

Man Years:
Total: 3 2/12
Professional: 1 5/12
Other: 1 9/12

Project Description:

A. Stability Studies

Six pools of the Edmonston strain of measles virus stored at -70°C have been periodically titrated for infectivity over periods ranging up to one year. The virus pools were prepared in KB cell cultures using Eagle's Basal Medium enriched with 5 to 20% inactivated calf serum. Under these conditions approximately 0.5 logs of virus were inactivated by the original freezing and thawing but little if any further loss was demonstrable for periods of storage up to one year.

One pool of virus prepared in similar fashion was lyophilized. Study of the dried virus over a four month period indicated a loss of approximately one log of infectivity in the original freeze-drying and reconstitution and no more than an additional 0.5 logs in the ensuing four months of storage at 4°C in the dried state.

These studies are being conducted primarily to determine the best method of storage for a reference measles strain. Information of this nature is also of value in predicting the probable stability of live measles virus vaccines.

B. Studies directed toward standardization of the measles virus neutralization and complement fixation tests.

Widespread interest in measles immunization has emphasized the

need for reliable procedures to detect and titrate measles antibodies. During the past year a study of variables in the test procedures has been made in order to form a basis for standardization.

Virus neutralization and complement fixation (CF) tests yielded generally comparable antibody titers although occasional sera devoid of demonstrable CF antibody were capable of neutralizing the virus. Neutralization tests employing 100 $TCID_{50}$ of virus based on a 12-14 day observation period afforded maximum sensitivity while maintaining reproducibility. Test designed for earlier termination (i.e. 6-8 days) required approximately 10 times greater amounts of virus in the inoculum, this resulted in a depression of serum antibody titer. Neutralization was largely complete in serum-virus mixtures by 1/2 to 1 hour at either 4° or 25°C and extension of the incubation time to 4 hours or more was not practical because of instability of the virus. Incubation of serum-virus mixtures at 37°C similarily resulted in excessive heat inactivation of virus.

The CF test was the procedure of choice in preliminary screening of sera since results were much more rapidly and easily obtained. Use of 4 or 8 rather than the conventional 2 units of CF antigen did not appreciably enhance sensitivity. CF antigens prepared from various cell culture types gave similar results when equivalent amounts of antigen were employed.

C. Studies concerned with production of measles reference antiserum.

Standardization of measles serologic procedures (as discussed in the preceding project subtitle) requires use of a standard antiserum as an internal control. Preparation of an antiserum of sufficient quantity and quality to serve as a national reference was undertaken and completed in 1960.

A simian source of serum was deemed most feasible. Data from a preliminary experiment employing sixteen naturally immune monkeys indicated that intramuscular inoculation with a mixture of measles antigen and Freund's incomplete adjuvant resulted in 16 to 32-fold increases in both neutralizing and CF antibodies. The immunizing antigen was prepared in simian kidney cell cultures, hence, the resultant hyperimmune sera were free of heterologous tissue antibodies.

Subsequently, 100 rhesus monkeys were immunized by this method and exsanguinated 1 to 2 weeks later. Their pooled sera were lyophilized in 0.5 ml amounts and are now available as a reference standard. The antibody titer of the final dried pool is approximately 1:1024 by our CF and neutralization procedures.

D. Evaluation of various features of attenuated and virulent measles strains in search for "markers" of attenuation.

Study in this area during the past year has been limited to preliminary evaluation of certain characteristics of four different passage levels of the Edmonston measles strain. One of these levels has been attenuated through chick embryo tissue passage, the other three have not and are presumably virulent.

Two points of difference have been noted thus far between the chick embryo adapted virus and the other viruses in studies employing stable cell lines. Harvests of attenuated virus regularly yield maximum titers of 10^4 or less per ml while the other passage levels yield 10^5 to 10^6 under identical conditions. In addition, potent CF antigens (titer 1:2 to 1:8) can be prepared with the virulent lines whereas such antigens cannot be prepared with the attenuated strain. In view of the observations described above it is of interest to note that the extent, speed and type of cytopathogenic changes produced by the chick embryo adapted strain are comparable to those observed with the other three strains.

E. Comparison of methods available for the primary isolation of virulent measles virus and recovery of tissue culture adapted and attenuated measles strains.

Primary isolation attempts have been unrewarding to date in our section due to lack of suitable clinical materials. We hope to obtain specimens from naturally infected children during the coming year in order to obtain data regarding the behavior of newly isolated measles strains in various host cell cultures.

During the past year a number of locally available stable cell lines have been evaluated in order to ascertain their relative sensitivity for the chick embryo adapted, attenuated Edmonston strain of measles virus. The HeLa and Hep-2 cells maintained by the Tissue Culture Section of the DBS are considerably less sensitive than the FL strain of continuous human amnion. The KB and monkey heart (Salk) stable cells available from Microbiological Associates, Inc., Bethesda, Md. are of comparable sensitivity to the FL amnion.

Several individual lots of living, attenuated measles vaccine (Edmonston strain) have been simultaneously tested by Dr. John Enders of Boston, Dr. M. R. Hilleman of Merck, Sharpe & Dohme and ourselves in order to compare host cell sensitivity. These tests included use of primary human amnion and kidney and the W-S stable human amnion by Dr. Enders, HeLa and primary green monkey kidney by Dr. Hilleman and monkey heart and FL stable human amnion in our section. Primary green monkey kidney and stable human amnion yielded the most consistently high virus titers although the other stable cells appeared only slightly less sensitive. The most striking observation was that primary human amnion and kidney were the least effective in virus detection.

These data suggest that primary human cell lines would be less desirable than the others tested for use in determining the potency (i.e. titer) of living measles vaccine.

Significance to Bio-medical Research and the Program of This Division.

Measles is a disease of considerable clinical and public health significance. The acute disease process is associated with an appreciable mortudity and mortality and in addition there is reason to suspect that measles infection may be frequently responsible for central nervous system damage. The prevention of measles consequently is a matter of enormous practical importance

Serial No. DBS_____

All work done by this Section pertaining to measles is directly concerned with one or another of the many problems associated with the development of measles vaccine.

Part B included Yes_____ No__X__

Serial No. DBS 36
1. Laboratory of Virology & Rickettsiology
2. General Virology Section
3. Bethesda, Maryland

PHS-NIH
Individual Projeet Report
Calendar Year 1960

Part A.

Project Title: Investigations Concerning the Spotted Fever Group of Rickettsiae

Principal Investigator: Dr. Harry M. Meyer, Jr.

Other Investigators: Nancy G. Rogers

Cooperating Units: None

Man Years:
Total: 10/12
Professional: 4/12
Other: 6/12

Project Description:

Study of a Rickettsial Agent Recovered from a Fatal Case with Unusual Clinical Features. In July of 1959 two cases of severe, fulminating disease occurred within a single family in North Carolina. Elucidation of the etiology of these infections, one of which terminated fatally, was of special interest because of their unusual clinical features.

Studies conducted with necropsy specimens obtained from the single fatal case resulted in recovery of a rickettsial agent. Isolation attempts were positive only in monkeys pretreated with cortisone and sulfisoxazole, not in guinea pigs or untreated monkeys.

Serologic procedures employing soluble-type rickettsial complement fixing (CF) antigens established that the isolate was a member of the spotted fever group of rickettsiae. Toxin neutralization procedures employing toxins prepared from the isolate and from the Bitterroot strain of Rocky Mountain spotted fever (RMSF) indicated that the agent was a strain of RMSF. The isolate is relatively avirulent for guinea pigs even after adaptation to that host and does not produce overt disease in mice.

Further studies are in progress in an effort to confirm the toxin neutralization data by complement fixation tests employing washed rickettsial (type specific) antigens.

Serial No. DBS____

Significance of This Project to Bio-medical Research and to the Program of This Division. This work serves to emphasize the protean features of RMSF and calls attention to the potential usefulness of cortisone and sulfisoxazole in increasing the susceptibility of animals to rickettsial infection.

Part B. Included Yes____ No X

Serial No. DBS 37
1. Laboratory of Virology & Rickettsiology
2. General Virology Section and Basic Virology & Rickettsiology Section

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Investigations Concerning Vacuolating Virus (VV)

Principal Investigator: Dr. Harry M. Meyer, Jr.

Other Investigators: Nancy G. Rogers, Hope E. Hopps and Barbara E. Brooks

Cooperating Units: None

Man Years:
Total: 1 6/12
Professional: 9/12
Other: 9/12

Project Description:

The vacuolating virus (VV or SV 40) discovered early in the year by Sweet and Hilleman (Live Polio Vaccines, Pan American Health Organization, Wash. D. C., 1960, 86-87) contaminant of rhesus kidney cell cultures. The agent multiplies to high titers in these cultures without producing cytopathogenic changes (CPE), and thus goes unrecognized unless the virus infected fluid is subinoculated into host cell cultures capable of showing CPE.

Current work has shown that several types of tissue cultures support the growth of the virus and develop characteristic CPE; these include kidney, ovary and testes cultures from vervet, grivet and patas monkeys (i.e. two subspecies of Cercopithecus aethiops and Erythrocebus patas). CPE has not been observed in the following cultures: primary rhesus and rabbit kidney, HeLa, KB, Hep-2, human amnion (FL), human liver (Chang), MAF, monkey heart (Salk) and stable rhesus monkey kidney.

Attempts are in progress to develop continuous cell lines from VV susceptible tissues of Cercopithecus aethiops. Testicular monolayers have been successfully propagated for six passages and renal cells for four passages.

Serologic investigations with VV appear encouraging. It has been possible to prepare potent CF antigens from both infected vervet (or

grivet) and rhesus kidney cell cultures. A satisfactory neutralization test has been developed using a challenge virus dose of 100 $TCID_{50}$ based on a 14 day test. In tests to date, there has been close correlation between the presence of CF and neutralizing antibodies in simian sera. Approximately 90% of sera tested from rhesus monkeys reaching the NIH have contained antibody for VV. On the other hand, no antibody was present in sera from 37 vervet and grivet monkeys reaching the NIH during the summer and fall of 1960, nor had any of these animals converted to positive by the time of their sacrifice (actually 1 to 2 months later.)

Significance to Biomedical Research and the Program of This Division. It is anticipated that this line of investigation will eventually prove valuable in selection of vacuolating virus-free monkeys for production of poliomyelitis and other vaccines.

Part B. Included Yes_____No__X__

Serial No. DBS 38
1. Laboratory of Virology & Rickettsiology
2. General Virology Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Investigations Concerning Lymphocytic Choriomeningitis (LCM) Virus

Principal Investigator: Dr. Harry M. Meyer, Jr.

Other Investigators: Nancy G. Rogers

Cooperating Units: None

Man Years:

Total:	8/12
Professional:	4/12
Other:	4/12

Project Description:
Evaluation of methods available for the detection of LCM virus. Work during the past year with the Jermain strain of LCM virus indicated that the standard LCM safety test employed on inactivated poliomyelitis vaccine could be made approximately 100 times more sensitive by inoculation of five guinea pigs rather than the conventional ten mice. The standard test involves intracerebral inoculation of 0.03 ml volume into each of ten mice with observation of the mice for death or disease for 21 days. A larger inoculum is used in the guinea pig tests, 0.1 ml intracerebrally and 5.0 ml intraperitoneally. Rectal temperatures are recorded daily for 21 days on each guinea pig and four to six weeks after inoculation the animals are bled out and their individual sera tested for complement fixing (CF) antibody for LCM virus. Small amounts of virus may infect guinea pigs without producing overt disease as indicated by a transient fever and the development of CF antibody.

Significance of this Project to Biomedical Research and to the Program of this Division. A safety test, designed to exclude the possibility of LCM virus contamination, is an integral part of the preparation of several viral vaccines. Work on this project is for the sole purpose of determining the most sensitive methods available for conducting the test.

Part . Included Yes___ No x___

Serial No. 39

1. Laboratory of Virology & Rickettsiology
2. General Virology Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Investigations Concerning Mumps Virus

Principal Investigator: Dr. Joseph P. O'Malley

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 4/12
Professional: 2/12
Other: 2/12

Project Description:

Development of a sensitive and reproducible method for determination of mumps virus neutralizing antibody:

Mumps virus was adapted to chick embryo cell cultures through serial passage. The cytopathogenic effect of the adapted virus on chick embryo monolayers was sufficiently pronounced to permit development of a plaque assay system. Preliminary work employing two human gamma globulin pools and two mumps immune sera indicate that this plaque assay system may prove useful for quantitation of mumps virus neutralizing antibody.

Investigation along these lines is being continued in order to compare the sensitivity and reproducibility of the plaque procedure with that of a virus neutralization test employing the conventional tube cultures.

Part B. included: Yes_____ No__x__

Serial No. 40

1. Laboratory of Virology & Rickettsiology
2. General Virology Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Investigations Concerned with Human Hepatitis Virus

Principal Investigator: Dr. Joseph P. O'Malley

Other Investigators: Dr. Harry M. Meyer, Jr., Miss Nancy G. Rogers

Cooperating Units: None

Man Years:
Total: 2
Professional: 1
Other: 1

Project Description:

Recovery and propagation of the etiologic agent or agents of human hepatitis in laboratory hosts:

A transmissible cytopathogenic agent has been recovered in rabbit kidney cell cultures inoculated with the NIH-6 icterogenic human plasma pool. The agent propagates readily in several types of primary and continuous cell cultures producing cytopathogenic changes but thus far has failed to cause disease or gross lesions in suckling mice, suckling hamsters, mice, guinea pigs, rabbits, embryonated eggs and Rhesus monkeys. No giant cells or inclusion bodies were observed in stained cell cultures showing cytonecrosis. Inactivation of approximately 100,000 $TCID_{50}$ of the agent at 37°C requires four weeks in citrated human plasma, although it is accomplished in 24 hours in medium 199. It passes through a 100 mu milipore filter but is retained by a 50 mu filter. Antisera for a number of known viruses as well as normal animal sera were devoid of antibody for the agent as determined by a plaque reduction neutralization test. Stored serial sera from 28 of 29 human volunteers inoculated several years ago with icterogenic plasma showed a four-fold or greater neutralizing antibody increase; 26 of these persons developed clinical hepatitis. Similarly, 7 of 10 volunteers who had received infectious hepatitis inocula developed a comparable rise in antibody. Sixty-six percent of sera were positive from 85 U.S. Navy personnel convalescent from a Naples 1959 infectious

hepatitis outbreak, whereas specimens from 400 consecutive normal blood donors were negative for neutralizing antibody.

Studies of the agent are continuing with primary emphasis on determining what role, if any, this virus may play in human hepatitis.

Significance to Bio-medical Research: The threat of serum hepatitis contamination of whole blood and blood derivatives as well as the continued significance of infectious hepatitis in civilian and military populations makes the control of these diseases one of the major unresolved problems of contemporary virology. If laboratory cultivation of the etiologic agent or agents can be accomplished, then effective control of human hepatitis becomes theoretically possible.

Part B. included: Yes_____ No__x___

Serial No. 41

1. Laboratory of Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Vacuolating Virus: Pathogenicity for Man

Principal Investigator: Dr. J. A. Morris

Other Investigators: C. G. Aulisio, K. M. Johnson, R. Chanock, V. Knight

Cooperating Units: Laboratory of Infectious Diseases and Laboratory of Clinical Investigations, NIAID

Man Years:
Total: 1/2
Professional: 2/6
Other: 1/6

Project Description:

Objectives: Determination of clinical and serologic responses in volunteers given vacuolating virus by respiratory route.

Methods: Standard clinical procedures developed by the Laboratory of Clinical Investigations, NIAID, for use in human volunteer work and conventional serologic methods employed in virus research.

Major Findings: Eight young adult volunteers were inoculated by the respiratory route with 2ml amounts of nebulized rhesus kidney cell preparation containing 10,000 $TCID_{50}$ of vacuolating virus (VV). The inoculum contained no other detectable virus. At the time of virus exposure none of the volunteers possessed neutralizing antibodies for VV in their sera; 3 weeks following virus administration all 8 had developed this antibody in titers ranging from 1:5 to $>$ 1:20. None

of the 8 developed signs of illness in the 4 months following virus administration. The virus was recovered from throat washings of two of the volunteers on the 7th day, and from another on the 11th day. Work of others (Sweet and Hilleman, Live Polio Vaccines, Pan American Health Organ., Wash., D. C., 1960, 86-87) suggest that VV administered orally fails to infect man. In contrast, the present findings indicate that inhalation of VV induces subclinical infection.

Significance to Biomedical Research and to the Program of this Division: Vacuolating virus is a frequent contaminant of primate cell cultures used in the preparation of poliomyelitis and adenovirus vaccines. Consequently, elucidation of its pathogenic potential for man is of special interest.

Part B. included: Yes_____ No__x__

Serial No. 42

1. Laboratory of Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Typhus vaccine - killed epidemic

Principal Investigator: Dr. J. Anthony Morris

Other Investigators: Calvin G. Aulisio, Elizabeth B. Jackson, Joseph E. Smadel, C. J. Wisseman, Jr.

Cooperating Units: Department of Microbiology
University of Maryland Medical School

Man Years:
Total: 11/12
Professional: 11/12
Other: 0

Project Description:

Objectives: To determine the antibody response in man and animals to immunization with (1) concentrated, purified epidemic typhus vaccine (2) combined epidemic typhus and Q fever vaccine.

Methods Employed: Standard procedures used in a research laboratory engaged in studies on rickettsiae.

Major Findings: A concentrated, partially purified epidemic typhus vaccine was prepared as described in reference 1, Part B. This material when stored wet or in the lyophilized state was shown to elicit good antibody responses in both man and animals. In the wet state the concentrated vaccine induced undesirable systemic effects in man (headache, fever) whereas the reconstituted dried vaccine elicited fewer and less intense systemic reactions. Experiments are planned to clarify the nature of the apparent change induced in the vaccine by the drying procedure.

Volunteer studies have been undertaken in cooperation with Dr. C. J. Wisseman, Jr. of the Department of Microbiology, University of Maryland Medical School, to examine the possibility of combining epidemic typhus and Q fever vaccines into a single immunizing preparation. Complement fixation and toxin neutralizing tests will be performed on sera obtained at appropriate times.

Significance to Biomedical Research and the Program of the Division: Rickettsial diseases might well become of importance throughout the world following devastations such as might be brought about by nuclear attack. It is therefore of importance that steps be taken to produce and stockpile stable and potent rickettsial vaccines.

Proposed Course of Project: Studies will be continued as outlined above.

Part B. included: Yes x No

Serial No. 42

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Smadel, J. E., Jackson, E. B., and Campbell, J. Studies on epidemic typhus vaccine. Arch. Inst. Pasteur, Tunis 36: 481-499, 1959. (Listed in 1959 report as in press).

Serial No.DBS 43
1. Laboratory of Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Study of Measles Virus and the Serologic Response of Experimental Animals to Measles Virus Propagated in Tissue Culture

Principal Investigator: Dr. Miklos N. Dreguss

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1 1/2
Professional: 3/4
Other: 3/4

Project Description:

Objective: To study the antigenic property of measles virus grown in tissue culture and to develop serologic procedures to measure antibodies directed against measles virus in sera of experimentally inoculated animals.

Methods Employed: Conventional procedures as used in virus research laboratories.

Major Findings: Measles virus (Edmonston strain) was propagated in eight different lines of cultured mammalian cells. In addition, preliminary attempts were made to grow the virus in cultures of chick embryo cells. Immune sera were prepared in rabbits, chickens, and guinea pigs by injection of infected cell cultures and the antibody in the resultant sera was measured by complement-fixation (CF) technique.

(a.) It was established that antigens prepared from culture fluids of measles virus, harvested on days 5 to 7, differed in their properties from antigens made of infected cell cultures and harvested on days 12 to 14. Guinea pigs inoculated with the 5 to 7-day material (phase A) responded with phase A antibody. These 2 antibody types could be distinguished one from the other by application of the CF

technique. There is cross reactivity between the antibodies directed against the two antigens, however, phase-A immune sera with a titer of 1:128 contain only little phase-B antibody (titer 1:16-1:32). Inversely, phase-B immune sera react at a higher dilution with phase-B antigen (1:128) than with phase-A. With passing of time, the antibody directed against phase-B antigen tends to diminish faster, while phase-A antibody is more persistent and its presence may be clearly demonstrated in the serum of guinea pigs up to 6 to 12 months following their immunization.

(b.) After injection of measles virus into guinea pigs by various routes, a mild fever response is observed during the 1st to 3rd week following inoculation. The CF antibody level in their serum reaches a titer of 1:32 to 1:128 within 3 or 4 weeks following a single injection, but the titer gradually decreases to about one-half to one-third of the original level in 4 to 6 months to become eventually negative in about a year. If two or more immunizing injections are given, early titers of 1:128 to 1:512 are recorded, then within a few weeks a decrease in titer is noted and it remains largely on this level for the next 8 to 12 months or longer.

(c.) Homologous or heterologous immune serum was injected intramuscularly, followed by inoculation with measles virus, in order to determine the effect of passively administered antibody on the serologic response to the virus. The fever response was suppressed and the antibody production was first at a very low level, however in some of the animals an increase of the antibody titer was noted 4 to 6 weeks later, in excess to that caused by the passively administered antibody. This indicates that both the homologous guinea pig immune serum and the heterologous antibody (Human gamma globulin) will slow down but does not completely prevent the antibody production to measles virus injected subsequently.

(d.) The CF-antibody level of pregnant guinea pigs immunized with measles virus at shorter or longer intervals before delivery has been compared with the antibody titer of their offspring in several litters. At the time of birth, the newborn animals showed practically the same antibody titer as their dams. At one month, largely the same level was maintained in both. Later, however, the titer in the baby animals decreased at faster rate than in their mother and reached quite low values in 3 months, while the antibody level in the mothers was better maintained during the same period. The baby guinea pigs were later subjected to inoculation with measles virus to determine the influence if any of the diaplacentally transmitted maternal antibodies. The serologic response was dependent on the time elapsed since the birth, and on the circulating antibody level at the time of this inoculation. The results were somewhat similar to the observations made after passively administered immune serum as mentioned under (c.).

(e.) Preliminary work was done on commercial human gamma globulin preparations to estimate their measles antibody content by indirect method. Gamma globulin solution was injected into guinea pigs i.m. and, a few days later, the animals were bled to titrate the measles antibody level in their sera by CF-test. The sera so obtained were not anticomplementary while gamma globulin solutions invariably are. Two days after injecting a 1:16 dilution of concentrated human gamma globulin, positive CF titers were noted against measles virus in 1:8, occasionally at 1:16 serum dilution. Additional work is needed to determine the value of using this method for practical purposes and to correlate it with immunizing potency.

Significance of this Study to DBS Program: The results of the research work reported here may furnish a useful tool for preliminary checking in the laboratory the antigenic value of experimental or commercial measles vaccines.

Proposed Course of Investigation: From the results herein summarized, it is clear that definitive characterization of the antigens present in measles culture fluids is required to define precisely the relative importance of the different antibodies obtained by immunization. The clinical significance of these antigens and antibodies also calls for detailed investigation. Expansion of the experimental work with respect to the use of immune gamma globulin is indicated to define, for practical purpose, the limits of its role in passive immunity to measles.

Part B. Included Yes_____ No X

Serial No. DBS 44
1. Laboratory of Virology & Rickettsiology
2. Division of Biologics Standards
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies on Photodynamic Resistance in Cell Cultures

Principal Investigator: Dr. Albert I. Holtz

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1/2
Professional: 1/2
Other: 0

Project Description:

Objectives: The mechanism of resistance to the photodynamic action of neutral red in cell cultures is being investigated.

Methods: Primary monkey kidney cells are grown in Leighton tubes, which have been covered with black tape to exclude ambient light. A fluorescent light has been designed which enables the experimenter to irradiate as many as 12 tubes at one time with light of controlled intensity. Cells are observed microscopically for photodynamic killing.

Work Accomplished: (1) Cells resistant to the photodynamic action of neutral red have been produced by incubation of cell cultures at 36°C in the dark with 1:50,000 neutral red for 24-30 hours. The presence of light is not necessary for the formation of photodynamic resistance. (2) Acridine orange and proflavine have been shown to produce resistant cells in the same way. (3) The formation of photodynamic resistance does not occur at 4 °C and is partially inhibited at 27.5°C. (4) The resistance to photodynamic action cannot be reversed by aeration of the cells or by the addition of fresh media. (5) Resistance is not due to the destruction of dye by the cells as the dye can be re-isolated and is photodynamically active when used again.

Serial No. DBS_____

Significance to D.B.S. Program: By investigation of the process o photodynamic resistance, information may be gained which can be applied to the photodynamic inactivation of adventitious agents in the oral polio vaccine. For example, it may prove possible to reduce the titer of the vacuolating agent in photodynamically resistant cells without damaging the ability of the cells to produce polio.

Part B included: Yes_____ No__x__

Serial No. DBS 45
1. Laboratory of Virology & Rickettsiology
2. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The etiology of the sarcomas associated with the cyst walls of Cysticercus fasciolaris in rat livers

Principal Investigator: Dr. Lawrence Kilham

Other Investigators: Dr. Louis J. Olivier

Cooperating Units: Laboratory of Parasitic Diseases NIAID

Man Years:
Total: 2/5
Professional: 1/5
Other: 1/5

Objectives: Sarcomas can be present in 100 percent of inbred rats infested with Tapeworm Larvae. These sarcomas may be due to (1) a carcinogen put out by the Cysticercus or (2) the localization of or activation of an oncogenic virus in the cysts. Both hypothesis will be explored. A further objective is to determine whether cats, which are the source of the tapeworms, have either circulating antibodies or the agent itself responsible for the oncogenesis. The possible etiologic agent under present study is Rat Virus (RV).

Methods Employed: General methods used in working with RV are discussed in a paper by Kilham, L. and Olivier, L. J., A Latent Virus of Rats Isolated in Tissue Culture, Virology 7: 428, 1959. Rats are given tapeworm infestations from cats. After the cysts have matured for nearly a year they have been ground and injected subcutaneously and intraperitoneally into newborn rats, hamsters and guinea pigs. Cats as received each week are bled and their kidneys removed for virus isolation and tissue culture.

Major Findings: Rat Virus (RV) was isolated from 2 rats bearing Cysticercus liver sarcomas. The other phases of the work are only just getting underway.

Significance of the Program to DBS: The problem concerns some of the central problems of cancer research, namely viral etiology and the possible role of carcinogens in a neoplasm of natural occurrence.

Part B. included: Yes____ No__x__

Serial No. DBS 46
1. Laboratory of Virology & Rickettsiology
2. Bethesda 14, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Latent infections and the pathogenesis of rat virus (RV) infections in hamsters and in multimammate rats

Principal Investigator: Dr. Lawrence Kilham

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 3/5
Professional: 2/5
Other: 1/5

Project Description:

Objectives: The aim of these studies is to learn more about the nature and behavior of Rat Virus (RV) in an effort to work out the mechanisms by which it induces mongolism as well as an acute fatal disease in hamsters. A further objective is to isolate Rat Virus (RV) from gern free rats and, if successful, to explore the possibility that this virus may be passed from mother to fetus in what has been termed "vertical" transmission from one generation to another.

Methods employed: The general methods of working with RV are given in the 2 publications of Part B. Aside from a study of the pathology of infected organs and titrations of their content of hemagglutinins and infective virus, an effort will be made to see if the acute fatal disease could be due to intravascular hemagglutination precipitated by viremia and whether the mongoloid dwarfism could have relation to Parotin, which is thought by some to be a hormone of the parotid gland. Further plans include the bleeding of germ free rats as removed from the tank and removal of their kidneys and spleens. Suspensions of the tissues are to be inoculated into newborn hamsters and into rat embryo tissue cultures and the sera tested for HI and neutralizing antibodies.

Major Findings: Suckling hamsters inoculated at from 1 to 4 days of age develop high titers of hemagglutinins and of infective virus in livers, kidneys and other organs as well as in the blood and urine. Mongolism develops in sucklings inoculated with minimal amounts of virus. A latent infection with considerable multiplication of virus but no disease takes place in older sucklings. Multimammate rats (Mastmys) develop diseases similar to those of the hamsters. As regards studies in germ free rats, sera from 30 of them have been found to contain HI-antibodies against RV.

Significance of Program to DBS: Rat virus has a number of properties which suggest that it is a member of the polyoma group of viruses. It is hoped that some method will develop from these studies whereby the possible oncogenic properties of RV can be demonstrated. Furthermore, the possibility that hamster mongolism may be of the same nature as human mongolism gives additional importance to investigations of this agent.

Latent infection and virus transmission from generation to generation are among the fundamental problems in the field of infectious diseases and, not improbably, of certain types of cancer as well.

Part B included: Yes /x/ No / /

Part B. Honors, Awards and Publications

Kilham, L., Olivier, L. J. A Latent Virus of Rats Isolated in Tissue Culture. Virology, 7: 428, 1959.

Kilham, L., Mongolism Associated with Rat Virus (RV) Infection in Hamsters. Virology (Accepted for Publication).

Serial No. DBS 47
1. Laboratory of Virology & Rickettsiology
2. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The potentiating effect of latent Trichinosis in rats on infection and disease due to EMC-virus

Principal Investigator: Dr. Lawrence Kilham

Other Investigator: Dr. Louis J. Olivier

Cooperating Units: Laboratory of Parasitic Diseases, NIAID

Man Years:
Total: 3/5
Professional: 2/5
Other: 1/5

Objective: This investigation grew out of studies made in Africa on an outbreak of EMC-virus infections as they involved wild animals, caged monkeys and one human case. As in other parts of the world rats of the genus rattus appeared to be vectors of importance. These animals, however, are resistant to infection. An objective of present studies is to find to what degree a common infection of rats, trichinosis, can break down their natural resistance to EMC-virus.

Methods Employed: The methods in general, are those outlined in the following publications. Kilham, L. et al., Pathogenesis of fatal encephalomyocarditis (EMC) virus infections in albino rats. Proc. Soc. Exp. Biol. Med. 90: 383, 1955. Kilham, L. et al. Host-virus Relations in Encephalomy (EMC) Virus Infections I and II., Am. J. Trop. Med. and Hyg. 5: 647 and 655, 1956. Additional methods are standard ones used for preparing, counting and inoculating the larvae of Trichinella spiralis.

Major Findings: In repeated experiments, adult rats have been divided into 3 equal groups. Those of group 1, which received T. spiralis alone have exhibited no disease and those of group 3, which have received EMC-virus alone (at a dilution of 10^{-4}) have also remained well. Group 2 rats were the ones inoculated with the same dose of virus 10 days after receiving T. spiralis. Up to 90% of these rats have developed a severe, crippling disease, fatal in many cases, and in comparison with the other 2 groups have experienced a sharp

and prolonged weight loss. EMC-virus has proliferated to high titer in the skeletal muscles of rats infested with T. spiralis but has not been recoverable from rats which received the virus alone.

Significance to the Program of the DBS: The fact that a latent infection with one type of organism can greatly alter the susceptibility to another and unrelated parasite should be a matter of consideration in the response of a host to any invading virus, whether the agent be given artificially or acquire entrance by natural modes of transmission.

Part B included: Yes / / No /x/

Serial No. DBS 48
1. Laboratory of Virology & Rickettsiology
2. Cancer Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Adaptation of Rat Virus (RV) and K-virus to Suckling Hamsters by Way of Hamster Embryo Tissue Culture.

Principal Investigator: Dr. Lawrence Kilham

Other Investigators: None

Cooperating Units: None

Man Years: None

Project Description:

The work has been completed and the project has been terminated. A description of the objectives, methods, and findings are given in the publications listed in Part B.

Part B.

Included Yes_____ No X

Serial No. DBS 49
1. Laboratory of Virology & Rickettsiology
2. Cancer Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Thermo-reproduction in Relation to Virulence of Viruses.

Principal Investigator: Dr. Lawrence Kilham

Other Investigators: None

Cooperating Units: None

Man Years: None

Project Description:

The work has been completed and the project has been terminated. A description of the objectives, methods, and findings are given in the publications listed in Part B.

Part B.

Included Yes X No____

Serial No. DBS 49

PHS-NIH
Individual Project Report
Calendar Year 1959

Part B. Honors, Awards, and Publications

Publications

Kilham, L. Relation of Thermo-resistance to Virulence Among Fibroma and Myxoma Viruses. Virology 9: 486-87, 1959.

Serial No. DBS 50
1. Laboratory of Virology & Rickettsiology
2. Cancer Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Processes of Cell Infection by Virus as Investigated by the Transformation Process and Viral DBAs: A Continuation of the Fibroma-Myxoma Studies.

Principal Investigator: Dr. Lawrence Kilham

Other Investigator: Dr. Joseph Shack (NCI)

Cooperating Units: National Cancer Institute

Man Years: None

Project Description:

The work has been completed and the project has been terminated. A description of the objectives, methods, and findings are given in the publications listed in Part B.

Part B.

Included Yes X No

Serial No. DBS 50

PHS-NIH
Individual Project Report
Calendar Year 1959

Part B. Honors, Awards, and Publications

Publications -

Kilham, L. The Fibroma-Myxoma Virus Transformation Recent Advances in Virus Research VII, pp. 101-127, 1960.

Serial No. 51
1. Laboratory of Virology
& Rickettsiology
2. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies on Antimicrobial Activity of Abalone Juice

a. Antibacterial
b. Antiviral
c. Antirickettsial

Principal Investigator: Dr. Chen Pien Li

Other Investigators: Drs. Benjamin Prescott
Albert I. Holtz
B. William Uhlendorf
Miss Elizabeth Jackson
Mr. William G. Jahnes

Cooperating Units: Bacterial Chemistry (NIAID)

Man Years:

Total: 7

Professional: 2

Other: 5

Project Description:

Objectives and Methods: The search for antiviral and antibacterial agents has been largely concentrated in the field of microbial products. However, the abundance and variety of organic materials in sea water, and the known ability of certain mollusks to filter and concentrate suspended solids of their aquatic millieu, led the investigator to study the abalone as a potential source of antimicrobial substances. The methods have been described in previous annual reports.

Work Accomplished:

1. The effect of canned abalone juice in experimental poliomyelitis in Swiss mice was studied by feeding the mice with the juice and then challenging them with one or another of the three types of poliovirus by intracerebral or intraspinal route. The rates of paralysis or death were 20 to 50% lower in the treated animals then in the controls. (See Part B)

challenging them with one or another of the three types of poliovirus by intracerebral or intraspinal route. The rates of paralysis or death were 20 to 50% lower in the treated animals then in the controls.(See Part B).

2. A limited number of sea animals were screened for in vitro antimicrobial activity against Staphylococcus aureus. The frozen fresh abalone juice and extracts of oysters and clams were found to possess marked inhibitory effect against this organism. Substances of this nature may be valuable therapeutic and prophylactic tools.

3. & 4. After the discovery of its antimicrobial activity the abalone juice was dialyzed and applied to the anion-exchanger diethylamino-ethycellulose (Cellex-D) column which was set up on an automatic fraction collector. The eluates were consecutively collected and pooled into 10 serial fractions. It was found that the early fractions of the series contained antibacterial activity against both penicillin-sensitive and resistant strains of Staphylococcus aureus, beta-hemolytic strain of Streptococcus pyogenes, Salmonella typhi, and paratyphi A and B. The growth of 10,000 or more organisms per ml was inhibited by this kind of fraction in a concentration of 10 mg. percent. These fractions showed no inhibitory activity in tissue culture against the tissue culture adapted Japanese 305 strain of influenza type A virus and a strain of the polyoma virus (isolated from mouse sarcoma 180 in our own laboratory). The fractions representing the later eluates including the final wash from the column with M NaCl contained no antibacterial activity. However, they showed definite inhibitory activity against influenza A virus and polyoma virus in tissue culture. In one illustrative experiment, inoculation of 10 $TCID_{50}$ of influenza A virus into a monolayer tissue culture of monkey kidney cells in 1 ml of medium 199 yielded 10^5 $TCID_{50}$ virus per 0.2 ml after 48 hours incubation at 35°C. When the cells were treated for 24 hours with 50 mg% of one of the later fractions before virus inoculation, virus multiplication could not be demonstrated at the end of two days.

It is clear then that there are two kinds of fractions; one kind is active against Staphylococcus aureus and certain other bacteria but not against polyoma virus and influenza virus while the other kind is active against these viruses but not against the bacteria. For the sake of convenience the first kind of fraction is designated as paolin 1 while the other kind as paolin 2. They are so designated because they were first isolated from abalone. The term "paolin" means in Chinese abalone extract.

Work in Progress.

1. Antibacterial activity. Experiments are being conducted to test the in vivo activity of paolin 1 on experimental streptococcal and pneumococcal infections in mice. Dr. Albert Holtz is largely responsible for this study. The results are very encouraging.

2. Antiviral activity. Recently we learned that the abalone juice we have been working on represents the abalone blood. A large number of fractions have been isolated by Dr. Prescott from abalone materials including the blood, using various methods. A substance similar to paolin 1 has also been isolated from oysters. Some of these fractions are being tested for antiviral activity in tissue culture and/or in mice. Influenza virus is used as one of the test agents. Dr. Uhlendorf is applying the metabolic inhibition test as a screening method for antiviral activity of these fractions.

3. The effect of paolin 1 and 2 on certain rickettsial infections in chick embryos and mice are being studied by Dr. Smadel, Miss Jackson and Mrs. Bernheim.

Part B Included Yes X No_____

Serial No. DBS 51

PHS-NIH
Individual Project Report —
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications

Li, C. P., Antimicrobial Effect of Abalone Juice.
Proc. Soc. Exp. Biol. Med., 1960, v103, 522.

Li, C. P., Antimicrobial Activity of Certain Marine Fauna.
Proc. Soc. Exp. Biol. Med., 1960, v104, 366.

Prescott, Benjamin, and Li, C. P.
Abalone Juice. Fractionation and Antibacterial Spectrum.
Proc. Soc. Exp. Biol. Med., in press.

Serial No. DBS 52
1. Laboratory of Virology & Rickettsiology
2. Respiratory Virus Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Influenza Viruses

Principal Investigators: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 2 1/6
Professional: 1/6
Other: 2

Objectives: The objectives of the project are to control and improve influenza virus vaccines and to improve methods for evaluating the safety, purity and potency of the product.

Early in 1960 the disease influenza abruptly increased, and excess mortality occurred due to influenza, pneumonia, cardiovascular and renal disease. Interest in immunization with influenza virus vaccines continued and there was an increase in the number of lots of vaccine submitted. From January 1960 to December 1960, 111 lots of influenza virus vaccines or influenza virus vaccines combined with adenovirus vaccines were submitted for release as compared with 62 lots of influenza virus vaccines submitted for release from December 7, 1958 to December 7, 1959.

Major Work on the Project: A. Potency tests on influenza virus vaccines. Potency tests for measuring the antigenic activity in mice were performed on 86 lots of influenza virus vaccines or the influenza virus components of combined influenza virus and adenovirus vaccines. Four lots of concentrated monovalent vaccine for report was tested by another method. B. Hemagglutination as a measure of viral content of vaccines. The CCA or chicken cell agglutination test that was adopted as a rough measure of viral content of lots of single strain vaccines for pooling in the manufacture of polyvalent vaccines is subject to many errors. The factors that influence this test are being determined and a simplified test is currently being investigated.

C. Reference standard for influenza virus vaccines. A new lot of influenza virus vaccine was assayed, a unit value was assigned to it, and it was adopted as a reference standard for the CCA test.

D. Studies on the antigenicity of current influenza virus strains. Because the antigenic composition of influenza virus strains that cause disease change every few years, a constant check on the strains currently causing disease is made and compared to the strains in the vaccines. During 1960, virus strains obtained from different areas appeared to be similar to the strains in the vaccines, hence no change in the vaccine strain formula have thus far been indicated.

Part B. Included Yes_____ No x

Serial No. DBS 53
1. Laboratory of Virology & Rickettsiology
2. Respiratory Virus Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Adenoviruses

Principal Investigators: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1 2/3
Professional: 1/6
Other: 1 1/2

Objectives: The objectives of the project are to control and improve adenovirus vaccines and to improve methods for evaluating the safety, purity and potency of the product.

Adenovirus vaccines have for several years been of interest to the military since new troops are particularly susceptible to adenovirus infections. During 1960 there has also been interest in adenovirus vaccines for the civilian population. During the year 33 lots of adenovirus vaccines or adenovirus vaccines combined with influenza virus vaccines were submitted for release. One additional manufacturer was licensed to sell adenovirus vaccines.

Major Work on the Project: A. Potency of adenovirus vaccines for types 3,4,7. Work on different methods for determining the potency of adenovirus vaccines has been continued. One method involving the immunization of guinea pigs and the use of their sera in a serum virus neutralization test in known numbers of HeLa cells was used to test adenovirus vaccines submitted for release.

B. Studies of susceptibility of tissue culture cells for the adenoviruses and inhibitors for the viruses in normal sera. These studies are of importance in safety tests of adenovirus vaccines. Eighteen lots of Hep 2 cells used for testing the safety of adenovirus vaccines were tested for sensitivity. Sera to be used in safety tests of adenovirus vaccines were tested for inhibitors for the three types of adenoviruses.

C. Reference vaccine. Monovalent vaccines for types 3, 4 and 7 were obtained and pooled (by Dr. Seligmann), according to different formula. The potency of each pooled lot was compared to a vaccine that had been used as a reference standard.

D. Purity. In experiments aimed at determining the presence of contaminating viruses in monkey kidney tissue cultures, the cultures used for production of adenovirus vaccines, extracts of the cells were given to newborn hamsters. After several months tumors developed and most of the animals died. The tumors were transplantable to other hamsters and they developed in 11 to 41 days. The tumors have some similarities to those produced by the polyoma virus but serologically they appear to be different. Information on the stability of this substance or agent is not yet available.

The general aim of the project is to fulfill the obligation of controlling and improving adenovirus vaccine. The proposed course of the project will follow along the same course as in 1960.

Part B. Included Yes_____ No X

Serial No. DBS 54
1. Laboratory of Virology & Rickettsiology
2. Respiratory Virus Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Vaccines for Multiple Respiratory Viruses

Principal Investigators: Dr. Bernice E. Eddy

Other Investigarors: None

Cooperating Units: None

Man Years:
Total: 3
Professional: 1/2
Other: 2 1/2

Objectives: This project is for the purpose of controlling multiple antigen vaccines, particularly vaccines made from different kinds of viruses. During 1960 a license was issued to another manufacturer for a vaccine made up of the four strains of influenza virus currently used in the influenza virus vaccine and three strains of adenovirus adsorbed on aluminum hydroxide. Standards are already available for influenza and adenovirus vaccines but the tests involve immunization of different species of animals by different routes.

Major Work on the Project. All of the problems that pertain to either influenza virus vaccines or adenovirus vaccines are pertinent to the control of the multiple vaccines plus some others. The adenovirus components are adsorbed on a precipitate and this could result in a loss of antigen if adsorption was not complete, or in instability of the antigenicity or in increased antibody due to the adjuvant effect of the precipitate. Thus far there is no indication that these factors are important although stability tests will have to be continued. Extensive potency tests have been carried out for both the influenza and adenovirus components. The general aim of the project is to fulfill the obligation of controlling and improving the combined adeno and influenza virus vaccines and in anticipating the need to control other multiple antigen vaccines having to do with respiratory disease. (For list of the total control work see separate page.)

Part B. included Yes_____ No X

Serial No. DBS_____

Control Work January 1, - December 1, 1960

Influenza virus vaccines submitted		
Civilian formula, four virus strains	68	lots
Military formula, six virus strains	21	
Combined Adeno and Influenza, four influenza virus strains	18	
Monovalent concentrates for export	4	
Total	111	

Adenovirus vaccines submitted		
Civilian formula, three virus strains	10	lots
Military formula, two virus strains	5	
Combined with influenza (see above) three adenovirus strains	18	
Total	33	

Tests completed for influenza virus strains

Swine on	10	lots
PR8	35	
Asian	35	
Great Lakes	31	
Lee	13	
Ann Arbor	48	

Tests completed for adenovirus strains

Type 3 on	26	lots
Type 4	31	
Type 7	31	

Tests underway on:

12 lots of Influenza Virus Vaccine
2 lots of Combined Influenza and Adenovirus Vaccine
1 lot of Adenovirus Vaccine

In addition did assay work on Adenovirus Vaccines and Influenza Virus Vaccines that were used for reference standards and carried out sensitivity test on 18 lots of cell cultures used for safety tests of Adenovirus Vaccines.

Serial No. DBS 55
1. Laborabory of Virology & Rickettsiology
2. General Virology Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Pneumococci

Principal Investigator: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total:
Professional: Insignificant
Other:

Objectives: The objective of the project is to control pneumococcus typing sera. This is a minor project; only three lots of pneumococcus typing sera were released in 1960.

Major Findings: A joint paper with Dr. F. Kauffmann and Dr. E. Lund on the nomenclature of the Danish and American types of pneumococci was published. See Part B.

The general aim of the project is to fulfill the obligation of controlling pneumococcus typing sera.

Part B. included Yes X No

1. Dmochowski, L., Grey, C. E., Stewart, S. E., Eddy, B. E., Burmester, B. R., and Walter, W. G. Morphology of cell constituents in tumors of viral origin. Cell Physiology of Neoplasia. Texas Press, in press.

2. Kauffmann, F., Lund, E., Eddy, B. E. Proposal for a change in the nomenclature of diplococcus pneumoniae and a comparison of the Danish and American type designations. International Bull. of Bact. Nomen. and Taxonomy 10:31-40, 1960.

3. Stewart, S. E., Eddy, B. E., Stanton, M. F. Progress in Virus Research. The polyoma virus. Experimental Tumor Research, 1: 67-84, 1960 S. Karger, Basel/New York.

4. Eddy, B. E., Borman, G. S., Kirschstein, R. L., and Touchette, R. H. Neoplasms in guinea pigs infected with SE Polyoma. Jour. Inf. Dis. In press.

5. Stewart, S. E., Eddy, B. E., Irwin, M., Lee, S., Development of resistance in mice to tumor induction by the SE polyoma virus. Nature No. 4725, 186: 615-617, 1960.

6. Eddy, B. E. The polyoma virus. Section B. Advances in Virus Research, 7: in press.

7. Three papers as follows condensed for the Yearbook of Cancer, 1959-1960 Series, Yearbook Publishers, Chicago.

Eddy, B. E., Stewart, S. E., Grubbs, G. E., Influence of tissue culture passage, storage, temperature and drying on viability of the SE polyoma virus. 453-455.

Eddy, B. E., Stewart, S. E., Kirschstein, R. L., and Young, R. D. Induction of subcutaneous nodules in rabbits with SE polyoma virus. 455-457.

Eddy, B. E., Stewart, S. E., Stanton, M. F., Marcotte, J. M. Induction of tumors in rats by tissue culture propagated SE polyoma virus. 457-458.

Serial No. DBS 56

1. Laboratory of Virology & Rickettsiology
2. Respiratory Virus Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Tumor Viruses

Principal Investigators: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1 1/6
Professional 1/6
Other: 1

Objectives: The objectives of this project are two-fold. 1) To isolate a virus or viruses from human neoplasms and to find a way to prevent neoplasms in man (the work was started in an effort to gain information on the etiology of lung cancer) and 2) To learn more about the adventitious substance in monkey kidney cell cultures that induces tumors in hamsters and something about it's stability.

Major Findings: Although work has been carried out with human tumor material, considerable effort has been expanded on the SE polyoma virus. This tumor virus was recovered in tissue culture from AKR mice, and an attempt is being made to use it, and also the tumors inducing substance in monkey kidney tissue cultures as a model for the recovery of a virus or viruses from human neoplasia. See Part B.
If lung cancer or any cancer is an infectious disease, there are prospects that a vaccine might be effective in preventing it. The propagation of the etiological agent is the first requisite for the preparation of such a vaccine.

Part B Included Yes X No

Serial No. DBS-57

1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Studies of the inactivation of viruses.

Principal Investigator: C. W. Hiatt, Ph.D. and Jerome J. Helprin, Ph.D.

Other Investigators: Dorothy Moore, B.A.

Cooperating Units: Section on Tissue Culture and Test Development, LVI, DBS.

Man Years:
Total: 3.33
Professional: 2.33
Other: 1.00

Project Description:

Objectives: (1) To gain information about the fundamental nature of the various biological properties of viruses through studying the mechanisms of inactivation of these properties by physical and chemical agents.

(2) To develop an understanding of processes of inactivation that may be applied to the preparation of viral vaccines.

Methods Employed: Various animal and bacterial viruses are cultivated in cell cultures and the infective fluids from these subjected to treatment with graded doses of the inactivating agent. Samples taken at the different dosage levels are assayed for infectivity, and the kinetic relationship between dose and survival ratio is established. From the characteristics of the survival curve inferences are drawn about the properties of the virus and the mechanism of the inactivating process.

Chemical and physical methods are used to investigate changes in structure and morphology of the virus particle, and immunological methods are used to investigate alterations in antigenic properties.

Major Findings: (1) Differential inactivation of simian viruses in suspensions of live poliovirus. It was earlier shown that irradiation of virus fluids with bright visible light in the presence of toluidine blue (1-10 ppm) would rapidly inactivate many animal viruses, but had virtually no effect upon poliovirus or other typical enteroviruses. Experiments showed that B-virus (Herpes simiae), when added to preparations of live poliovirus, could be destroyed by this method without appreciable loss of the poliovirus. Extending these observations, we have found that some other viruses of simian origin (SV-1, SV-6, SV-12, SV-15, and vacuolating agent) are also amenable to this method of selective inactivation. One of the simian agents, SV-16, is very highly resistant to photodynamic inactivation with toluidine blue, suggesting that this agent may be an enterovirus.

(2) Development of continuous-flow irradiation equipment. A water-jacketed helix of glass tubing surrounding a tubular incandescent light source has been used for continuous-flow irradiation of fluids with visible light. This apparatus had been calibrated previously with a 40-watt light source, using suspensions of T3 coliphage sensitized with toluidine blue (6 ug/ml) as an actinometer and was shown to be capable of killing 5 logarithmic units of phage infectivity at a flow rate of 12 ml/min. With a 1000-watt light source, the flow rate was found to be more than 500 ml/min. and with the 1500-watt light source presently available is calculated to be greater than 800 ml/min.

Three lots of monkey kidney tissue-culture fluid containing endogenous vacuolating agent (10^3 infectious units/ml) have been processed in the 1500-watt apparatus at a flow rate of 150 ml/min. No vacuolating agent was found in any of the treated fluids when ordinary volumes were tested.

(3) Mechanism of photodynamic inactivation of bacteriophage. T2r+ coliphage particles treated with toluidine blue and visible light and collected by centrifugation were found to contain less DNA than control preparations. Electron micrographs disclosed that phage ghosts were formed during irradiation, the individual particles having lost DNA through leakage in an undetermined manner. The rate of ghost formation was much slower than the observed rate of photodynamic inactivation, however, indicating that a more subtle mode of inactivation precedes the loss of DNA.

(4) Basis for the resistance of poliovirus to photodynamic action. Poliovirus grown in the presence of proflavine (5 ug/ml) or toluidine blue (3 ug/ml) did not become photosensitive, as might have been expected if the protective effect of the protein coat is primarily responsible for the resistance of poliovirus to photodynamic action. Poliovirus RNA, however, when separated from the protein coat, is highly susceptible to photodynamic inactivation with toluidine blue. With these two apparently contradictory findings, no conclusion may yet be drawn as to the essential basis for the resistance of intact poliovirus.

(5) Permeability of viruses to photodynamic dyes. For T2r$^+$ coliphage, the rate of photodynamic inactivation is believed to depend upon the concentration of dye in the "inner compartment", i.e., within the envelope of the protein coat. From Arrhenius plots of inactivation data, the energies of activation for permeation of this phage with toluidine blue and proflavine were calculated as 28.3 and 10.6 kcal./mole, respectively. This indicates that the viral membrane is much more restrictive against toluidine blue than against proflavine.

In similar studies, neutral red was found to have an energy of activation of 4.2 kcal/mole for permeation of T3 coliphage. The other dyes tested (toluidine blue and proflavine) enter this phage too rapidly for kinetic studies.

Among the animal viruses studied, ECHO-10 (Reovirus) is the only one showing restricted permeability. The slow permeation of toluidine blue into the sensitive portions of this virus is suggestive of the presence of an organized membrane. The Arrhenius energy of activation for uptake of toluidine blue is 7.6 kcal/mole.

Significance to the Program of DBS. The continued investigation of the mode of action of viral inactivants is expected to contribute to the fundamental basis for control of viral vaccines. In particular, the method for differential inactivation of simian viruses may find an important application in the manufacture of live poliovirus vaccine.

Proposed Course of Project. This project will be continued.

Part B included Yes /X/ No /__/

Serial No. DBS-57

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Hiatt, C. W., Kaufman, E., Helprin, J. J., and Baron, S., 1960 Inactivation of viruses by the photodynamic action of toluidine blue. J. Immunol. 84:480-484.

Hiatt, C. W., 1960, Photodynamic inactivation of viruses. Trans. N. Y. Acad. Sci.

Serial No. DBS-58
1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Physical and chemical characterization of viruses.

Principal Investigator: C. W. Hiatt, Ph.D.

Other Investigators: John F. Thiel, B.A., Raoul J. Benoit, Jr., B.S.

Cooperating Units: None

Man Years:
Total: 1.08
Professional: 1.08
Other:

Project Description:

Objectives: To obtain information about the physical dimensions and chemical composition of animal viruses and to correlate this information with biological properties.

Methods Employed: Standard methods of physical and chemical analysis, including ultracentrifugation and electron microscopy, are supplemented by specialized techniques for concentrating and purifying viruses.

Major Findings: (1) Determination of sedimentation constant from infectivity measurements. Apparatus has been designed and partially constructed to permit the use of six partition cells in the same ultracentrifuge rotor. The distance of the partition from the center of rotation is different in each cell. In a single centrifuge run with a given virus suspension six estimates of the boundary position may be made based upon relative infectivity of the contents of the upper compartments. This equipment will be used to determine approximate S values for newly isolated animal viruses.

(2) Preparation of viruses for electron-microscopy: A comparative study has been made of methods for concentrating and purifying small volumes of virus suspensions specifically for electron microscopic observation. Adsorption upon red blood cell stroma, direct sedimentation upon the microscope grid and purification by membrane filtration are the three methods which seem to offer the greatest promise.

Significance to the Program of DBS: The development of methods for rapid characterization of newly isolated viruses will assist in the testing of viral vaccines for safety and purity.

Proposed Course of the Project: This project will be continued.

Part B included Yes /__/ No /X/

Serial No. DBS-59

1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Development of methods for the chemical analysis of biological products.

Principal Investigator: C. W. Hiatt, Ph.D.

Other Investigators: Robert Blereau, B.S.

Cooperating Units: None

Man Years:
Total: None
Professional:
Other

Project Description: This project was terminated in 1959 upon completion of a report for publication.

Part B included Yes /X/ No /__/

Serial No. DBS- 59

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications.

Publications other than abstracts from this project:

Hiatt, C. W., and Blereau, R., 1960, Nephelometric assay of protein in tissue culture vaccines. Drug Standards (Accepted for publication).

Serial No. DBS- 60

1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Effect of sunlight on the molluscicidal activity of sodium pentachlorophenate.

Principal Investigator: C. W. Hiatt, Ph.D

Other Investigators: Louis J. Olivier, Ph.D., Willard T. Haskins, Ph.D.

Cooperating Units: Laboratory of Tropical Diseases, NIAID.

Man Years:
Total: None
Professional:
Other:

Project Description: This project was terminated in 1959 upon completion of a report for publication.

Part B included Yes /X/ No /__/

Serial No. DBS-60

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Hiatt, C. W., Haskins, W. T., and Olivier, L., 1960, The action of sunlight on sodium pentachlorophenate. Am. J. Trop. Med. and Hyg. 9:527-531.

Honors and awards relating to this project:

None.

Serial No. DBS- 61

1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Properties of the sera of guinea pigs inoculated with diphtheria toxoid and Freund's adjuvant.

Principal Investigator: C. W. Hiatt, Ph.D.

Other Investigators: Sara E. Branham, M. D., Ph.D.

Cooperating Units: Laboratory of Bacterial Products, DBS.

Man Years:
Total: None
Professional:
Other:

Project Description: This project was terminated in 1959 upon completion of a report for publication.

Part B included Yes /X/ No /__/

Serial No. DBS- 61

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications

Branham, S. E., and Hiatt, C. W., 1960, Properties of diphtheria antitoxins produced in guinea pigs with the use of Freund's adjuvant. Proc. Soc. Exp. Biol. Med. 104:484-486

Honors and awards relating to this project:

None.

Serial No. 62

1. Laboratory of Blood & Blood Products
2. Blood & Blood Derivatives, Diagnostic Reagents
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Development and Application of Control Procedures for Blood and Blood Products.

Principal Investigator: Dr. John T. Tripp

Other Investigators: Dr. David L. Aronson
Miss Marietta Carr
Miss Ann L. Dayton
Mr. Joel M. Solomon
Dr. Richard T. Suchinsky
Dr. Mitsuo Yokoyama

Cooperating Units: None

Man Years:

Total:	2.9	Patient Days:	None
Professional:	2.0		
Other:	0.9		

Project Description:

Objectives: To develop improved control procedures and standards by evaluating the present control procedures and manufacturing methods as these affect the safety, purity, and potency of biologic products derived from blood.

Methods Employed: (a) Samples of biologic products derived from blood are sent as unknowns to manufacturers or blood banks for comparative testing utilizing new methods and reagents as well as standard techniques.

(b) Colored photographic slides of agglutination reactions are interpreted on a voluntary basis by blood bank technicians in a study of blood banking errors. The technicians record their results on forms supplied by the laboratory as well as on their routine forms.

(c) A study of bacterial contamination of blood and derivatives of blood is being carried out in order to determine the mode of action of bacteriological filter pads and filters. These materials are immobilized by collodion imbedding to allow thin sections to be taken for microscopic examination.

(d) To increase the efficiency and precision of control tests requiring serial dilutions, the variability and optimal operating conditions of a recently redesigned proportional diluter is being investigated.

(e) To determine the efficiency and applicability of shipping containers for blood and other materials requiring storage at low temperatures various containers are packed as for shipment and a continuous record is made of the temperature using a recording potentiometer. In addition information during actual shipment conditions is being obtained.

(f) An attempt is being made to develop methods of identifying allergenic extracts by hyperimmunization of rabbits.

(g) To investigate and compare the equilibria of hemagglutination reactions of the ABO blood group system, percentages of cells left unagglutinated by mono- and multispecific antisera after various periods of time are determined hemocytometrically.

(h) Infrared spectrometry is being utilized to determine changes occurring in plastic blood containers resulting from age, temperature and humidity.

(i) This is a study to identify the globulin fractions containing the agglutination activity of various antibodies. Continuous flow electrophoresis is employed to fractionate the proteins. Immunophoresis and paper electrophoresis are used to identify the proteins in each fraction.

(j) Various techniques and instruments are being studied for the purpose of development of two dimensional immunophoresis.

Major Findings:

(a) Though the evaluation of blood bank techniques is a continuing project no evaluation was carried out during this year.

(b) The study of blood banking errors has been completed with about 100 blood bank technicians recording approximately 40,000 readings. The data has not yet been tabulated or analyzed for significance.

(c) The investigation of filter materials is continuing but there have been no major findings to date.

(d) Further minor improvements were made in the proportional diluter. This project has been discontinued.

(e) An expanded plastic container that has high heat efficiency and is low in price has been evaluated. Work continues on the study of containers frozen shipments and on portable refrigerators utilizing light weight mechanical refrigeration.

(f) The study of allergenics has not yielded any significant results. This work has been discontinued due to emphasis on other projects.

(g) The study of the quantitation of antibodies has been discontinued because of the resignation of the employee interested in this work.

(h) Very little effort has been put on the study of changes in plastic blood containers with the result that there have been no significant observations made.

(i) The antibodies of the ABO group have been studied. The results are being tabulated for publication.

(j) Using a square frame of antibodies impregnated filter paper on the agar has produced a pattern that promises to improve identification of identical antibodies and beta globulin. In addition a full covering of filter paper has produced good delineation of the numerous antigen-antibody systems. A report for publication is in preparation.

Significance of Research:

As part of the responsibility of the Laboratory in the control of products derived from blood these investigations can lead to improvements in control procedures resulting in greater significance and specificity of the tests.

Proposed Course of Project:

All parts of this project will continue along the same lines with the exception of those noted as having been discontinued.

Part B included Yes /x / No / /

Serial No. 62

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Haberman, S., Aguilar, E., Solomon, J. M. and Tripp, J. T. The Reliability of Anti-Human Serums in the Detection of ABO Hemolytic Disease of the Newborn. Am. Jour. of Clin. Path., 34: 179-184, 1960.

Serial No. 63
1. Laboratory of Blood & Blood Products
2. Blood & Blood Derivatives
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Stability and Potency of Blood Fractions.

Principal Investigator: Dr. John T. Tripp

Other Investigators: Dr. David L. Aronson
Miss Ann L. Dayton
Mr. Paul O. Fehnel
Dr. John S. Finlayson
Dr. Sandor S. Shapiro
Dr. Richard T. Suchinsky

Cooperating Units: None

Man Years:
Total: 5.0
Professional: 3.2
Other: 1.8

Patient Days: None

Project Description:

Objectives: To delineate the changes occurring in the physical and chemical properties of various human plasma proteins resulting from the physical and chemical treatment incidental to processing and to investigate the properties, the mechanisms of action, and methods of assay of blood coagulation components and related systems.

Methods Employed: (a) Parallel samples of liquid and dried Normal Serum Albumin (Human) are stored at 32°C., 5°C., and ambient room temperature. At regular intervals the materials are tested for stability by viscosity determinations, ultracentrifugation, electrophoresis, and nephelometry.

(b) In order to study the effects of physical and chemical treatment of plasma derivatives these products are being subjected to heating to 60°C. ultraviolet irradiation and long-term storage. Column chromatography with continuous pH and ionic strength gradient elution is being utilized to separate various fractions of albumin following the treatment. The chromatographically separated fractions have been studied by ultracentifugation and by other physical and chemical tests to find evidence of changes in the protein.

(c) To gain further insight into the clotting mechanism, changes in the

biologic activity of certain clotting factors, such as prothrombin, are being investigated at oil/water interfaces.

(d) The effect of bovine fibrinolysin on fibrinogen is being studied utilizing routine clotting methods.

(e) The sensitivity of dried proteins to ionizing radiation appears to be a direct function of molecular size. This method, utilizing low voltage electron irradiation, is being utilized to study molecular weights of several blood coagulation system factors in an impure state.

(f) Starch gel electrophoresis is being used to study prothrombin.

(g) Column chromatography with both DEAE and amberlite IR-50 is being used with some success in the purification and characterization of components of the coagulation system in order to define the necessary and sufficient conditions for normal coagulation and for clot destruction.

Major Findings: (a) Periodic routine stability measurements have been performed during this, the sixth year of the study. Definite changes, still of unknown clinical significance, have again been observed in albumin stored at temperatures over 5°C.

(b) The chromatography -ultracentrifugation technique has proved to be a reproducible and sensitive tool. When chromatographically separated regions of human albumin were again subject to chromatography in the same system, they were eluted by the same conditions as in the original chromatogram, indicating a real chemical difference between albumins. Albumin heated in the presence of stabilizers at 60°C. for ten hours behaved chromatographically essentially the same as that of untreated albumin. However, albumin heated in the absence of stabilizers led to large amounts of material appearing later in the elution pattern. This material was shown in the ultracentrifuge to be of higher molecular weight. A definitive study on plasma has been completed and published.

(c) Measurements of the properties of clotting factors at oil/water interfaces have not actually been made pending purification of the coagulation factors to be studied. This has now been done.

(d) The study of a useful fibrinolyic assay based on blood clotting methods has been discontinued due to the resignation of the interested investigator, however the work is being prepared for publication.

(e) Additional measurements have been made on components of the blood clotting system and previous tentative results have been confirmed. Work on prothrombin and thrombin has been completed. The molecular weight of thrombin has been determined to be 32,000 when dried from the frozen state and 64,000 when samples are air dried at room temperature. The molecular weight of antihemophilic globulin is now estimated to be 150,000 and that of plasma thromboplastin component to be about 90,000.

(f) The study of prothrombin by starch gel electrophoresis has been completed. A publication is in preparation.

(g) A prothrombin of high specific activity has been prepared by ultracentrifuge and paper electrophoresis. It is essentially homogeneous. It is free of factor X but contaminated with factor VII. A fibrinogen, free of fibrinolysin, has been prepared and preliminary studies have been made on the purification of anti-hemophilic globulin.

Significance of Research:

All blood and blood products controlled by Division of Biologics Standards are required to be stable and potent. Improved methods for the evaluation and assay of these characteristics in vitro are being developed to improve our ability to determine stability and potency and to place these control functions on a foundation of knowledge gained through research.

Proposed Course of Project:

The various parts of this project will be continued.

Part B included Yes /x / No / /

Serial No. 63

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Finlayson, J. S., Suchinsky, R. T. and Dayton, A. L. Effects of Long Term Storage on Human Serum Albumin I. Chromatographic and Ultracentrifugal Aspects. J. Clin. Invest. 39: 1837-1840, 1960.

Suchinsky, R. T. A Study of Eight Heated Plasma Protein Preparations. J. Clin. Invest. 39: 1953-1962, 1960.

Serial No. 64
1. Laboratory of Blood & Blood Products
2. Blood Bank, Diagnostic Reagents
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Development and Application of Immunohematological Research Procedures.

Principal Investigator: Dr. Allan Kliman

Other Investigators: Dr. John S. Finlayson
Mrs. Eleanor G. Morrison
Mr. Joel M. Solomon
Dr. Mitsuo Yokoyama

Cooperating Units: None

Man Years:
Total: 2.0
Professional: 1.5
Other: 0.5

Patient Days: None

Project Description:

Objectives: The objectives of this project are to search for the rare antibodies to the human blood factors which results from the antigenic stimulus of pregnancy, transfusion, and natural exposure; to develop better methods for this work and its application to clinical and laboratory medicine.

Methods Employed: (a) Blood samples from random blood donors, transfusion recipients, anthropological and disease groups, as well as patients presenting specific problems are screened for rare antigens and antibodies using tools and techniques developed in this laboratory as well as those exchanged with other workers.

(b) Intensive study is made of specific examples from the above screening procedure with the aim of making recommendations for specific therapy in individual cases and to obtain broad guidelines for use in the control of biologics. Serological methods are corrolated with transfusion experiments in sensitized subjects using chromium 51 tagged red cells.

(c) To determine whether isoagglutinin titers in patients with specific diseases are an index of antibody forming potential, measurements are made by serial dilution on normals and patients with various diseases such as rheumatoid arthritis and dysproteinemias. The antibody response to various injected antigens is measured.

(d) The immunological and chemical properties of fractions collected after ion exchange fractionation of blood group antibodies is being determined. Standard immunohematological methods are used for the detection of the antibodies.

(e) Rabbits and chickens are being used for the production of antisera to rare blood group antigens. These antisera are studied by electrophoretic methods in addition to absorptive, elution and inhibition techniques.

(f) A study of the varying abilities of animals to produce anti-human serum is being carried out by immunization with differing sera and by different methods. The animal sera have been studied by immunophoresis.

(g) The control and prevention of hepatitis among transfused patients is an important objective. Blood from donors associated with cases of hepatitis is collected and screened by all available liver function tests. In addition, the ability of the donor's blood to neutralize hepatitis viruses in tissue culture is being studied.

Major Findings: (a) Screening of all interesting blood samples from various sources has continued. Over 1600 complete genotypes have been performed on various blood samples to attempt to establish the incidence and mode of inheritance of antigens.

(b) Interesting cases discovered during the screening of blood samples have been studied intensively. This has led to specific recommendations applicable to the routine preparation of blood for transfusion.

(c) It would appear that, in some diseases such as chronic lymphatic leukemia, there is a correlation of isoagglutinin titers and total gamma globulin levels. However in acute leukemia there appears little correlation between isoagglutinin titers, antibody forming potential and serum gamma globulin levels. Agammaglobulinemia exhibits a low gamma globulin and low isoagglutinin titer whereas macroglobulinemia and multiple myeloma show an increase in abnormal proteins but a decrease in isoagglutinin titers.

(d) Preliminary findings of the separation of blood group antibodies on cellulose columns indicate there are distinct differences in serologic activities among the different types of antibodies.

(e) The production of animal antisera to various blood group antigens is still being carried out. It has been found possible in many cases to prepare appropriate antisera.

(f) The study of the varying abilities of animals to produce anti-human sera has shown that there is also variation in the specificity of antibody response.

(g) In the study of hepatitis, data has been collected during the year. However, no conclusions have been drawn as yet from the study.

Significance of Research:

It is necessary for this Division to be aware of the expected effects from the many minor incompatible transfusions which must occur among the over 5,500,000 transfusions of blood each year in this country. The research effort attempts to pin-point some of the more important aspects of these exposures to foreign antigens.

Proposed Course of Project:

It is expected that all aspects of this project will be continued during the next year.

Part B included Yes /x / No / /

Serial No. 64

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Fahey, J. L. and Morrison, E. Separation of 6.6S and 18S Gamma Globulins with Isohemagglutinin Activity. J. Lab. Clin. Med. 55: 912-916, 1960.

Shaw, R. K., Szwed, C., Boggs, D. R., Fahey, J. L., Frei, E., Morrison, E. and Utz, J. P. Infection and Immunity in Chronic Lymphocytic Leukemia. Arch. Int. Med. 106: 467-478, 1960.

Shohl, J., Fahey, J. L., Morrison, E. and Schmidt, P. J. Studies on Isohemagglutinins in a Variety of Dysproteinemias. Proc. VIIIth Cong. Int. Soc. Blood Transfusion, Sept. 1960.

Serial No. 65
1. Laboratory of Blood & Blood Products
2. Blood Bank
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Stability and Potency of Formed Blood Elements.

Principal Investigator: Dr. Allan Kliman

Other Investigators: Mrs. Eleanor G. Morrison
Dr. Paul J. Schmidt

Cooperating Units: None

Man Years:
Total: 0.6
Professional: 0.6
Other: 0.0

Patient Days: None

Project Description:

Objectives: To establish standards of potency for the antigenicity and viability of the formed blood elements.

Methods Employed: (a) Erythrocytes with the Rh_o variant (D^u) blood factor are being tested for antigenicity by transfusion to females over 50 years of age or to males who are receiving transfusions as part of their prescribed therapy. Differential agglutination techniques are employed in following the survival of the transfused cells. Antibody screening and identification is being carried out.

(b) A program to study the use of platelet transfusion in thrombocytopenic states in leukemia employs platelet concentrates and platelet rich plasma in large doses. The effect on the recipients platelet count and on his clinical course is studied. The effects of donating platelets at frequent intervals are studied by detailed repetitive tests on the donor's blood.

(c) To establish a reserve of rare types of red cells for transfusion to sensitized patients, rare donor red cells are collected, frozen by the glycerol method and deglycerolized when needed for transfusion.

(d) The properties of white blood cells are being studied by transfusion into patients who exhibit repeated febrile non-hemolytic transfusion reactions. Patients are given transfusions on separate occasions of washed red cells, the buffy coat and fresh plasma all from the same donor.

(e) The relationship between methods of blood collection and preservation and some of the physical characteristics resulting from these methods is being established. Storage in liquid nitrogen of red blood cells, white cells and platelets is being investigated.

Major Findings: (a) Over 70 transfusions of Rh$_o$ variant (D^u) blood have been given. No antigenicity of these selected units has been demonstrated.

(b) Large doses of platelet concentrates and platelet rich plasma from a single donor were effective in stopping hemorrhage and reversing the generalized bleeding tendency of children with leukemia without side reactions. Donation of the platelets from two pints of blood two times a week for three months did not harm the donors and provided information to support the use of plasmapheresis as a means of obtaining platelets.

(c) A stockpile of rare red cells has been established for transfusion needs. Blood for transfusion has been supplied in quantity for patients with rare group-type combinations. As a corollary, data for standards concerning the purity, potency and safety of glycerolized red cells for transfusion are being collected.

(d) In the study of white blood cells it has been found that reactions may occur in the absence of leukoagglutins and many patients with leukoagglutins never have reactions. Patients do not usually react in a reproducible manner to the same donor.

(e) Using Ackeroyd's solution Reagent Red Blood Cells may be stored in liquid nitrogen more conveniently than in glycerol for routine laboratory use. Antigenic integrity is well preserved. This project is also yielding information necessary for standards governing the purity and potency of red cells stored in liquid nitrogen.

Significance of Research:

The standards for blood products which this laboratory must establish must be based on practical experience in handling these products. Applications for licensing of these products then can be evaluated realistically. Experience gained in establishing requirements for the various formed elements of blood has immediate value in the functions of the Division of Biologics Standards. In addition, projects such as the evaluation of the antigenicity of Rh$_o$ variant (D^u) and leucocytes will assist in determining the significance of these products in clinical use and the needs for their control when applications are received.

Proposed Course of Project:

All aspects of this project will be actively pursued as yielding vitally needed information.

Part B included Yes /x / No / /

Serial No. 65

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Schmidt, P. J. and Steinfeld, J. L. The Effect of Resuspension and Shipment on the Viability of Frozen Red Cells. Clinical Science, 19: 109-118, 1960.

REPORT ON OTHER THAN RESEARCH OR CLINICAL ACTIVITIES OF
LABORATORY OF BLOOD & BLOOD PRODUCTS

In addition to the research activities designed to support control functions, that are outlined in the accompanying project reports the Laboratory of Blood and Blood Products has carried out its primary function of controlling the safety, purity and potency of blood and blood products. Among these control functions are the following:

1. Control testing of the various blood and blood products produced by 154 licenses operating 225 principle locations and 217 donor centers and other subsidiary facilities. These licensees hold 586 product licenses for blood and blood products. This control testing includes all of the physical, chemical and immunological testing found necessary for action on the various blood products submitted for licensure and release. In 1960 control testing involved over 2100 lots of blood products including 440 inspection samples.

2. As required by regulations each establishment producing blood products was inspected at least once during the year. In fiscal 1960 the qualified inspectors performed a total of 404 inspections requiring 366 man days away from the laboratory. During this past year there have been 10 qualified inspectors available to perform this work in addition to their other duties.

3. License application for 20 blood products were reviewed and the licenses were granted. Six licenses were granted for establishments for blood and blood products and there are 8 licenses pending.

4. Labels and circulars were reviewed for all biological products from licensed manufacturers. Over 400 groups of labels and circulars were received and reviewed for compliance with the regulations. This work involved the labels and circulars from 188 licensed establishments which are licensed for 279 different biological products and who hold 1231 active product licenses each having its own labels.

5. Reference standards are maintained for 7 blood products. Work has been started on 10 new preparations for ultimate adoption.

6. This Laboratory has devoted a significant amount of time to the preparation of regulations for the control of various blood products. Drafts have been prepared for regulations for 6 products that will be proposed for adoption upon completion of revision of the general regulations. Additional Standards for Packed Red Blood Cells (Human) have been submitted for initial publication in the Federal Register. Additional Standards for Heparinized Whole Blood (Human) are awaiting final publication in the Federal Register.

7. The blood bank serving the needs of patients in the Clinical Center is operated as a Section of this Laboratory. The blood bank provides the specialized knowledge for other staff of the Laboratory of Blood and Blood Products. At the same time the other units of the Laboratory, in observing the day-to-day needs of an operating blood bank, can maintain a more realistic attitude toward regulatory functions. Over 6000 units of blood were processed in the blood bank in 1960 for patient care either in the form of whole blood or as special blood derivatives. Emphasis is still being placed on the im-

portance of fresh blood to support surgery utilizing extracorporeal circulation. The need for platelets in the study of leukemia has resulted in increased use of plasmapheresis. Much is being learned regarding this technique for the separation of formed elements and from these very practical considerations valuable information is available for the control program of the Laboratory.

8. A panel of typed donors is maintained among NIH employees. This panel consisting of 743 persons serves as a source of extensively characterized red cells for many of the control and research programs of this laboratory. Without this panel of donors it would not be possible to carry out many of the control tests necessary in the regulation of the production of blood products.

Annual Report of Activities
Division of General Medical Sciences
Calendar Year 1960

SUMMARY STATEMENT

During the past year the Division of General Medical Sciences has grown in program activities, and its budget has nearly doubled.

In accordance with the original plan in the establishment of the Division in July 1958, DGMS has the administrative responsibility for the grant programs in the basic medical and biological sciences, in environmental and public health, and in certain clinical areas not covered by the programs of the Institutes. The Division also administers the grant programs for training investigators in the basic biomedical sciences, provides fellowships for general research training, directs the Russian Scientific Translation Program, the NIH Center for Aging Research and the General Clinical Research Center Program.

The Division is headed by G. Halsey Hunt, M.D., and Frederick L. Stone, Ph.D., continues as Assistant Chief and Chief of the Research Training Branch.

Budget

The following table summarizes the growth in budget of the Division over the past three years:

	F.Y. 59	F.Y. 60	F.Y. 61	F.Y. 62 (Est.)
Research Grants	$16,621,000	$23,559,000	$36,844,000	$33,643,000[1/]
Training Grants	6,040,000	13,040,000	27,000,000	26,500,000
Research Fellowships	3,260,000	5,310,000	10,100,000	10,100,000
Review & Approval	817,000	1,280,000	2,019,000	1,665,000[1/]
Administration				471,000
Clinical Research Centers			5,000,000	12,000,000
Total	$26,738,000	$43,189,000	$80,963,000	$84,379,000[1/]

PERSONNEL

At the end of calendar year 1959, there were 69 persons in the Division. At the end of calendar year 1960, there were 103 persons, assigned as follows:

1/The estimate for F.Y. 1962 does not include environmental health, a total comparable amount of $9,333,000, of which $164,000 is for Review & Approval and $9,169,000 for Research Grants.

Office of the Chief	8
Administrative	12
Information	5
Research Training Branch	44
Research Grants Branch	25
Russian Translation	3
Center for Aging Research	6
Total	103

Major Personnel Additions

Maurice E. Odoroff
Assistant to the Chief, DGMS

Joseph H. Gerber, M.D., D.P.H.
Director, Center for Aging Research

Carl R. Brewer, Ph.D.
Chief, Research Grants Branch

Frederick P. Ferguson, Ph.D.
Chief, Research Fellowship Section,
Research Training Branch

Ronald E. Scantlebury, Ph.D.
Chief, Foreign Grants and Awards Program

J. Harold Upton Brown, Ph.D.
Executive Secretary, Physiology Training Committee,
Research Training Branch

Raymond W. Cunningham, Ph.D.
Executive Secretary, Pathology Training Committee,
Pharmacology Training Committee,
Research Training Branch

Everett F. Davis, Ph.D.
Executive Secretary, Regular Research Fellowships,
Research Training Branch

F. Ellis Kelsey, Ph.D.
Program Analyst, Research Grants Branch

George McKray, L.L.B., M.P.H.
Program Analyst, Research Grants Branch

Herbert B. Pahl, Ph.D.
Executive Secretary, Biochemistry Training Committee,
Biophysical Sciences Training Committee,
Research Training Branch

Guy W. Moore
Deputy Information Officer, DGMS

Joe Evelyn Graber, M.P.H.
Information Officer,
Administrative Officer, Center for Aging Research

RESEARCH GRANTS

During the past year the research grants branch has supported activities in six major fields through more than 1,257 grants in an amount exceeding $23.5 million.

Chemistry of Life Processes, including biochemistry, pharmacology, metabolism, nutrition, immunochemistry, toxicology, etc. Approximately 25 percent of DGMS research grant funds are going into this area.

Developmental Biology, including physiology, cell biology, genetics, reproduction and development, microbiology, histology, etc. Approximately 25.5 percent of DGMS research grant funds are going into this area.

Clinical Sciences, including endocrinology and pathology, and other fundamental problems related to the clinical care of patients. Approximately 9.5 percent of DGMS research grant funds are going into this area.

Environmental Factors in Health and Disease, including air pollution, water pollution and sewage disposal, food technology and contamination, occupational medicine, radiation, industrial health hazards, etc. Approximately 22 percent of DGMS research grant funds are going into this area.

Public Health, Medical Care and Nursing, including development of epidemiological and biometrical methods applicable to large scale investigation of disease, studies of nursing procedures, the role of the nurse in communicable disease control, etc. Approximately 10 percent of DGMS research grant funds are going into this area.

Methods and Tools of Science, including biophysics, instrumentation and methods, biometry and statistics, conferences, handbooks, publications, etc. Approximately 8 percent of DGMS research grant funds are going into this area.

December 31 Level of Activity

As of December 31, 1959, 1,190 research grants were paid, totaling $20,003,057. As of December 1960, 1,470 grants were paid, totaling $25,151,754.

Analysis of DGMS Research Grants

An analysis of grants by DGMS reveals that the Division awarded 1,130 research grants to schools in fiscal year 1959 and 1,242 in fiscal year 1960. Another 12 percent, or 142 grants in fiscal year 1959 and 143 in 1960, went to research foundations and institutions not connected with a university.

The greatest percentage for both years went to universities, exclusive of medical schools, public health schools, nursing schools, etc. The universities received 375 grants in fiscal year 1959 and 421 in fiscal year 1960, about 33 percent of the total for both years.

Medical schools received the second largest number of DGMS grants. In fiscal year 1959, they were awarded 312, and in fiscal year 1960, 325 grants. This was roughly 27 percent of the total.

Sixteen other types of schools were recipients of DGMS grants, including liberal arts colleges, technological schools, marine laboratories and forestry and agriculture schools.

General Clinical Research Center Program Established

During the past year the General Clinical Research Center Program was established by DGMS. This was in accordance with directions by the Senate Committee on Appropriations in 1959 to help meet national needs for an improvement and intensification of clinical research throughout the Nation.

The general program is to be distinguished from the program of clinical research centers being supported by the Institutes of the NIH, which was authorized in the fiscal year 1961 appropriation. The programs of the Institutes are categorical -- that is, concerned primarily with one disease or group of diseases, such as heart disorders or cancer, toward which the work of a particular Institute is oriented.

The DGMS program is more general, giving participating institutions the opportunity to carry out research in a variety of different fields, with basic and clinical skills being focused on a broad spectrum of diseases and fundamental scientific problems. The program provides means for precise observations and control of research with patients and for extending laboratory research in animals into valid correlative studies in human beings.

The Clinical Research Center Section of DGMS handles those applications for general clinical research centers coming under the responsibility of the Division, and conducts preliminary negotiations and staff visits; aids in the review of grant applications; assists the National Advisory Health Council in matters concerning the General Clinical Research Center Program; answers professional queries concerning the program, and maintains continuing liaison with established Centers. Sam Silbergeld, M.D., Ph.D., was named chief of this section in October 1960.

Grants are given to institutions such as medical schools and research hospitals for the establishment of special research centers or facilities. The grant funds pay for the renovation and equipment of facilities, the cost of the care of research patients, supporting laboratories, and certain staff salaries.

During calendar year 1960, upon the recommendations to the Surgeon General by the National Advisory Health Council, 19 such research grant awards were made to medical schools by DGMS. The total dollar volume of these awards was $7,484,110, which included funds from both the 1960 and 1961 fiscal year appropriations.

Russian Scientific Translation Program Transferred to DGMS

In April 1960 the Russian Scientific Translation Program was transferred from the Division of Research Grants, NIH to DGMS. The Program administers the translation of Russian papers, journals and other printed matter pertaining to medicine and biology, and makes them available to American scientific audiences.

Environmental Health Program

DGMS is assigned the bulk of the NIH responsibility for research grants in the fields of air and water pollution. Because these programs have been funded under dual appropriations (Sanitary Engineering Activities and General Research and Services), the Research Grants Branch and the Office of the Chief, DGMS, have worked in close cooperation with the Bureau of State Services in administering grants in these areas. In April 1959 the House Appropriations Committee called upon PHS to carry out a study on environmental health problems and on the most efficient organization of facilities to meet these problems. Present plans call for the establishment of a new Bureau of Environmental Health, and the transfer of the program which this past year gave more than 300 grants totaling more than $5,800,000 in the fields of accident prevention, air pollution, milk, food, interstate and community sanitation, occupational medicine, radiation and water pollution.

RESEARCH TRAINING GRANTS

Growth of Training Grants Program

The growth of the DGMS program for research training grants from 293 grants at $12.7 million in calendar year 1959 to 436 grants at $20.6 million in calendar year 1960 reflects a greatly expanding program.

DGMS was supporting research training programs in two major areas at the beginning of calendar year 1958; eight, at the end of 1958; ten, at the end of 1959; and eleven at the end of 1960. These were in addition to limited amounts of programming in other important areas which do not yet have regular, full-fledged Training Committees.

Microbiology Training Program Established

A Microbiology Training Program was established in DGMS and held its first meeting in January 1960. Chairman of the group is Dr. Morris F. Shaffer, Chairman, Department of Microbiology, Tulane University School of Medicine, New Orleans, Louisiana.

This program is designed to support training at predoctoral and post-doctoral levels in medical schools, schools of public health, veterinary schools, other recognized graduate schools, research institutions and hospitals.

Physical Biology Training Program Transferred to DGMS, and Renamed

The Physical Biology Training Program of NIH was transferred from the National Institute of Arthritis and Metabolic Diseases to DGMS in June 1960, in keeping with administrative realignments being made in program responsibilities at NIH. The program supports graduate research training in the biophysical sciences.

In October 1960, the name of the Physical Biology Training Program was changed to Biophysical Sciences Training Program. The change is designed to emphasize the program's broader approach to interdisciplinary studies embracing the concepts and methodologies of both biology and the physical, chemical and mathematical sciences. The program supports training leading toward research in a variety of biophysical fields such as radiation biology, physical properties of (and interactions between) macromolecules, theoretical biology, and the dynamics of structure-function relationships.

The Training Committee held its first meeting under its expanded mandate of activities and laid long-range plans whereby research training programs in the biophysical sciences will be able to receive support in schools where such specialized training can best be provided.

Developmental Biology

In June 1960 the name of the Embryology and Development Training Program was changed to the Developmental Biology Training Program, to indicate more fully the Division's concern for the wide range of interests and pursuits covered by the areas of cellular and developmental biology.

Research training activities encompassed by this title could be of a multidisciplinary nature based largely on modern anatomical, biochemical and physiological approaches. Included are studies of fine structure, immunology, experimental and comparative embryology, cellular physiology, and all other fields which contribute importantly to the elucidation of cellular or developmental mechanisms at fundamental levels. Comparative embryological training using the above disciplinary approaches aimed at various phylogenetic levels, including the human, also will be included in the broad training area of responsibility intended for this program.

Review of Evaluation of Experimental Training Grants

The Program Directors of the Experimental Training Grants Program (ETG) met at the University of Pittsburgh School of Medicine in March 1960 to discuss the current status of the program, which has been under way since 1956, and to consider the evaluation study in progress. The meeting was in relation to the 13 grants which have been awarded by DGMS to 13 schools for studies in furthering the training of students for careers in academic medicine.

Dr. Edward W. Dempsey, Washington University School of Medicine, was chairman of the session. DGMS was represented by Dr. Frederick L. Stone, Assistant Chief of the Division, and Dr. L. Edgar Lee, Executive Secretary of the ETG program. The preliminary evaluation report was presented by Dr. John T. Cowles, study director of the ETG evaluation program and professor of psychology at the University of Pittsburgh School of Medicine.

Dr. Cowles' report summarized data on attitudes and activities of medical students with a view toward aiding the schools in their efforts to find new approaches to the preparation and development of talented medical students for research and teaching careers. The data thus far have been taken from the school records of 2,574 students and from questionnaires answered by 2,328 students. Further studies were to be made of those students showing an exceptional interest in research and those who have made the fullest use of the opportunities made available through the program.

The ETG program is aimed at solving two related problems: (1) how to provide a greater number of undergraduate medical students with training which would more adequately prepare them for careers in academic medicine; and (2) how to strengthen the university relationships of the medical schools in the basic science areas, perhaps through the introduction of new disciplines or new points of view into the medical faculties.

Dr. Cowles' report, to be published early in 1961, is expected to shed considerable light on the question whether at the end of its five-year period, the program should be extended, curtailed or continued at the same level. At least two things were apparent from preliminary findings: (1) if more students are to be encouraged to participate in research, more time and money should be provided; (2) there is no doubt that participation in research in medical school under the Experimental Training Grants Program has influenced favorably the career plans of students by arousing or confirming interest in an academic career.

Foreign Grants and Awards Program

In April 1960 the Foreign Grants and Awards Program was transferred from the Division of Research Grants, NIH, to DGMS. This program, headed by Dr. R. E. Scantlebury, administers the Foreign Grants and Awards Program and the Visiting Program.

Research Fellowships

This program has grown from 810 Fellowships at $3,402,357 in calendar year 1959 to 1,413 Fellowships at $6,855,418 in 1960. The funds, provided under the General Research and Services appropriation, are defended by DGMS in the appropriations hearings and are included in the DGMS program although Research Fellowships continue under dual management by DGMS and the Division of Research Grants.

The Senior Fellowship Grant Program is intended to encourage and support the development of professional personnel for academic and research careers in medicine, dentistry, public health, and related areas, and to aid in stabilizing careers in such fields. Candidates are selected on the basis of demonstrated promise for careers in independent research and teaching.

Grants are awarded for five-year periods and are renewable in certain instances for an additional three-year period, and are paid to the grantee institution for salary, expenses of the fellow directly related to the purposes of the award, and indirect costs on the total of these two items.

The Special Fellowship Grant Program is intended to provide advanced or specialized training to assist in the development of a research and academic career in medicine, dentistry, public health and related areas. These grants will support the young investigator not yet eligible for an award at a higher level. Each application is reviewed by a committee of nongovernmental scientists and by an appropriate National Advisory Council.

The Career Research Professor Program of DGMS awards career research professorship grants to medical schools, dental schools or schools of public health to (1) establish additional full professorial positions in medicine, dentistry, public health and related areas, and (2) assist in recruiting into these positions persons with the most thorough training and the greatest aptitude and promise for productive careers in research and teaching and (3) provide still further incentive for the choice of a career devoted to research and teaching on the part of the young scholars.

A list of fellowships obligated as of the end of calendar year 1959 and 1960 shows:

Calendar Year 1959

Fellowships:	Number	Amount
Predoctoral	68	$ 254,408
Postdoctoral	31	187,161
Special	8	47,317
Part-time	356	230,688
Postsophomore	115	434,559
Senior	182	1,903,257
Foreign	50	344,967
	810	$3,402,357

Calendar Year 1960

Fellowships:	Number	Amount
Predoctoral[1/]	551	$1,913,823
Postdoctoral	117	684,773
Special	19	149,883
Part-time	325	210,584
Postsophomore	144	566,915
Senior	198	2,882,798[2/]
Foreign	59	446,642
	1,413	$6,855,418

CENTER FOR AGING RESEARCH

The Center for Aging Research, a component of DGMS, serves as the NIH focal point for extramural research in aging. The Center stimulates and assists the development of new research projects in gerontology at universities, medical centers and various other research institutions in this country and abroad; maintains liaison among Federal agencies and other organizations supporting programs in aging; fosters the training of additional research personnel; collects and disseminates data related to research in aging; and sponsors conferences, symposia, and seminars on research and training problems in the field of aging.

The increased national interest in this field and the concentration of effort on stimulating new projects has been greatly responsible for the significant increase in the number of projects supported. Currently, more than 800 projects are considered to relate to the various aspects of aging, as compared to 274 projects in 1958. During this same period of time, funds supporting this research have grown from $4,570,424 to more than $16,000,000.

Activities of CAR

Emphasis among grantees and potential grantees is being directed to increased study in the three broad areas which are embraced by research in aging: the behavioral and social sciences, the clinical sciences, and the biological sciences. These research activities seek to provide answers to questions relating to the older person's mental health, physical well-being, and to the very basic questions relating to the exact nature of biologic processes and their relation to disease.

During the year the staff reviewed approximately 15,000 grant applications received by NIH. Those pertaining to aging were categorized and

1/Includes Nurses -- 66 @ $296,770.
2/Includes $397,192 from DGMS research grant funds for support of the $7,500 research allowance.

filed pending action by the Advisory Councils. When acted upon by the Advisory Councils, the applications are incorporated into the Center's active files. With the background information contained in the Center's extensive files, the professional staff undertakes project site visits to places where potentially fruitful additional research in aging may be undertaken -- of the fifty site visits made this year, twenty were in the interest of stimulating new research projects.

Multidisciplinary Research

CAR is continuing to provide assistance to university and medical school groups which wish to develop collaborative research programs. In addition to the two programs established at Duke University (1957) and Albert Einstein College of Medicine (1958), two new programs were approved and put into operation during calendar year 1960. These were at Western Reserve University, Cleveland, Ohio, inaugurated in May 1960; and the University of Miami School of Medicine, Coral Gables, Florida, inaugurated in September 1960.

The program at Western Reserve University involves the entire University and several affiliated hospitals. Principal attention is being given to chronic disease, particularly in conjunction with studies on rehabilitation. Investigations into the basic biological changes in aging are being carried out also.

At the University of Miami School of Medicine the program will be entirely basic in its approach to aging. It involves the medical school, the main University, and the marine biology laboratory in related studies in anatomy, physiology, biochemistry, microbiology, botany and related sciences.

Program Units

It has been recommended by the CAR and its consultants that more university-wide Centers be established, though not necessarily of the magnitude of those now in existence. Similar Centers, called Program Units, might be established in 40 or 50 institutions throughout the country. The objectives of such Program Units would be to provide mechanisms for stimulating and integrating research interests in aging in atmospheres of common scientific pursuits. In addition to the research which could be carried out by such units, periodic institution-wide seminars of the various aspects of aging would be conducted, and training opportunities and teaching activities would be fostered. The overall plan calls for long-term support for such Units.

Conferences

Of particular importance this year has been CAR work done in connection with the White House Conference on Aging, January 9-12, 1961. Dr. Stanley R. Mohler has served in the capacity of Technical Director to the

Committee on Research in Gerontology: Medical and to the Committee on Research in Gerontology: Biological. A wide distribution of the background papers prepared by each of these committees was made by CAR.

The agenda for the Conference was planned with the assistance of the CAR staff, which also provided advice in selecting the key work-group participants.

Among the other national and international meetings which were assisted and attended by the staff of the Center for Aging Research during calendar year 1960 were: The Fourth Annual New England Conference on Aging, in Woodstock, Vermont; The Institute of Advanced Behavioral Science Research, in Berkeley, California; the Fifth International Congress of Gerontology in San Francisco, California; the American Dietetic Association Congress in Cleveland, Ohio; the Pan-American Medical Association Conference in Mexico City; the American Medical Association Meeting in Miami, Florida; the American Sociological Association, New York; the National Committee on Aging, New York; and the American Public Health Association in San Francisco, California.

The following papers were given by staff members of CAR at these meetings: "Current Gerontological Research," Dr. Gerber, Fourth Annual New England Conference on Aging; "Nutritional Aspects of Medical Research for the Aging," Dr. Gerber, American Dietetic Association; "Problems of Gerontology in the U.S.," Dr. Mohler, Pan-American Medical Association; "Aging and Pilot Performance: Current Related Research and Research Needs," Dr. Mohler, Postgraduate Course in Aviation Medicine.

Grant funds in the amount of $80,000 were provided jointly by DGMS and the National Heart Institute to sponsor the Fifth International Congress in Gerontology. Many of the delegates to the Congress were also in attendance at the Institute of Advanced Behavioral Science Research in Berkeley. Funds to provide the transportation of certain delegates to the Berkeley meeting were made possible by a grant from the National Institute of Mental Health. Thirty-one countries were represented at these two meetings.

Cooperation with Other Agencies

Frequent meetings have been held with the Federal Aviation Agency in connection with its research grant program to investigate the relationship between aging and the performance of pilots.

Information Activities

During 1960 informational work in aging included preparation and publication of three brochures: "Research Highlights in Aging," "Activities of the NIH in the Field of Gerontology," and "Summary of NIH Research Programs in Aging;" press releases; fact-finding and background papers; information statements, etc.

A total of nearly 20,000 pamphlets, press releases and other information items were distributed by the Information Office, DGMS, between January and September 1960. A distribution of 17,000 copies of the three main publications has been made: 2,000 copies of "Activities of the NIH in the Field of Gerontology," 6,000 copies of the "Summary of NIH Research Programs in Aging," and 9,000 copies of "Research Highlights in Aging." These figures include distribution at the White House Conference on Aging.

Since the appointment of an Information Officer to CAR in October, office routines for the operation have been established and all informational activities pertaining to research in aging have been delegated to CAR.

DGMS INFORMATION OFFICE

During the past year the DGMS Information Office functions were expanded somewhat in keeping with the Division's increased activities. The number of professional persons engaged in information and/or reporting work increased from two to six. Of this total, three are assigned to the Office of the Chief; two to the Research Grants Branch; and one to the Center for Aging Research. Tentative plans call for the employment also of an information person to be assigned to the Training Branch.

Activities

In addition to its program-related activities in the preparation of the Opening Statement, Weekly Report, Annual Report of Activities, etc., the Information Office prepared and/or edited and/or distributed six pamphlets related to the Division's programs in research and training and to aging. In addition, work was completed on a brochure on DGMS and all of its programs. This will be off the press in February 1961.

Fourteen press releases and 41 professional announcements were issued on the Division's work, on subjects such as the establishment of new programs, the acquisition of new personnel, important grants in training and research.

The following table indicates the quantity and areas of distribution of these materials by mail and through various conferences:

	Number of Copies		
	Scientific[1/]	Other[2/]	Totals
6 Pamphlets	20,069	1,094	21,163
14 Press Releases	14,600	3,432	18,032
41 Professional Announcements	15,200	2,750	17,950
	49,869	7,276	57,145
		Grand Total	57,145

This brief report does not include the distribution of nearly 2,000 copies of Gestation, by Dr. Jack Davies, M.D., which DGMS sponsored, or the distribution of reprints of speeches and scientific papers by DGMS personnel. Also in the interest of brevity, only a mention is made here of the Information Office's work in handling mail and telephone inquires and requests; in the preparation of speeches, or of summaries or reports for internal or limited use; in contacting the universities and medical schools in relation to public relations matters; and in performing various other DGMS and NIH staff functions.

# # #

1/Professional journals, deans and department heads of medical, dental, public health and veterinary schools, Training Committees, Study Sections, National Advisory Councils, science conferences, science writers, professional requests, etc.

2/Congress, newspapers, paramedical publications, lay requests, etc.

Annual Report of Program Activities
Division of Research Grants
Calendar Year 1960

Summary Statement

The Division of Research Grants continued to serve in 1960 as the center for administering the grant and award programs of the National Institutes of Health. In terms of projects and funds awarded from the fiscal year 1960 budget, the Division provided processing, review and fiscal services for 11,572 research project grants totaling $198.7 million; 3,729 fellowships, $14.8 million; and 171 health research facility construction grants totaling $30.8 million. The Division also provided fiscal audit services for 526 traineeship awards, totaling $3.0 million, and 2,626 training grants amounting to $73.7 million.

The year was highlighted by several major personnel changes. On November 14, Dr. Ernest M. Allen, Chief of the Division and Associate NIH Director for Research Grants, was given full-time staff responsibility as Associate Director in the Office of the NIH Director. Dr. Dale R. Lindsay, formerly Assistant Chief, DRG, was reassigned as Chief. Also reassigned was Dr. Clinton C. Powell, formerly Assistant Grants Branch Chief for Clinical Research, to the post of Deputy Chief of the Division.

During the year the Division assumed administrative responsibility for the NIH training grant and traineeship programs. A training section was established with responsibilities paralleling DRG activities in the research grants area: receiving, assigning and distributing applications; reviewing budget requests of applications; establishing policies and procedures for payment and management of training grants and awards; maintaining central records; establishing training grant review committees where requested, and other duties involving liaison.

On May 27 the NIH Director approved establishment of the Division's 36th study section--Medicinal Chemistry. The study sections, whose primary function is to provide initial review of research grant applications, also continued their program activities by stimulating and planning an increased number of meetings and institutes to exchange, gather and publish information on specific health and medical problems.

Also established in 1960 was the Advisory Committee for Computers in Research, composed of biologists, physicists and experts in computer technology.

The Health Research Facilities Program began its fifth year of operation in July. As of October 1, 1960, 212 research facilities constructed under this program were completed and in use. These represent Federal expenditures of $28.6 million and a total construction cost of over $139 million.

The Research Fellowships Review Branch changed the composition of its review panels so that outside specialists now review and evaluate regular fellowship applications. In the past this process had been carried out by NIH research personnel. Additionally, the number of these disciplinary review panels was increased from nine to ten to help accommodate the sharp increase in the number of applications. Near the end of 1960 the entire Fellowships Program was modified and expanded to meet changing needs of the scientific community. As a result the Branch has been assigned new responsibilities for development of policies, rules and procedures for the Career Research Professorship Grants Program, the Senior Research Fellowship Grants Program, and the Special Fellowship Grants Program.

Information Office

The DRG Information Office functions as a component of the Office of the Chief, DRG, and is staffed by an Information Officer, two information specialists, a secretary and a clerk-typist. Its responsibilities include the planning and executing of a broad program of information on the policies, activities and achievements of the NIH extramural programs.

Recipients of such information include the Congress; NIH, PHS, and DHEW administrators and those of other Federal and quasi-Federal agencies (such as the Science Information Exchange); administrators of private foundations, universities, hospitals and medical schools; both grantee and non-grantee members of the medical and allied professions; professional journals; the lay press; radio and TV, and the general public.

During the year the office expanded a number of activities and added several new ones. The increase in requests for speech preparation and numerous other writing services, from upper echelon NIH, PHS and DHEW officials as well as from within DRG, made necessary the employment of a new staff member for assignment to this specific area. Consultative services were expanded to accommodate requests from other divisions of the PHS; for example, substantial help was provided to the Division of General Health Services, BSS, on two exhibits on research in public health. Distribution of the bi-weekly administrative publication, "DRG DIGEST" was expanded to include key personnel in the grants branches of the various Institutes. An extensive effort was made by the Information Office during 1960 to strengthen relationships with public information officers in grantee institutions, and a new file on current programs and activities in these institutions was established in the Information Office.

The office continued in its responsibilities for preparing annual and special reports for the Congress; writing and distributing press releases; preparing weekly reports to the Surgeon General on program developments; handling voluminous public inquiries by telephone and correspondence; providing editorial assistance as required; handling clearances of manuscripts; and other general information services.

Research Grants Review Branch

During the year, the Research Grants Review Branch continued its steady expansion and growth, as an expression of the continued increase in the number of applications received and the increasing multiplication and ramification of the entire extramural program structure.

Organizational Changes

The number of study sections increased to 36 with the elevation of the Advisory Committee on Medicinal Chemistry to study section status. This was the culmination of the Division's recognition of the need to identify this facet of medical research preceptors, i.e., the general field of organic chemistry as it pertained to medical research.

The growing need for policy guidance and review function in the field of computers, especially as they apply to medical research and medical practice, necessitated the organization of an Advisory Committee on Computers.

Internal reorganization, which is a continuous thing in a dynamic group, shifted the Renewal Notice Function from the Grants Administration Section to the Project Control Section. This puts both ends of the job (going and coming - notice and receipt) in the same unit with a common records source.

New Post Created

During the past year, the new position of Deputy Chief was created as a consequence and in recognition of the expanded work load. This officer shares with the Chief the responsibility for making the initial breakdowns in the project assignment system and for the regular daily tasks. He also has responsibilities in connection with such functions as conferences and symposia, and for guidance in Special Study Section matters and ad hoc review.

Grants Management Branch

Scope of Activity

The Branch's activities, related to the management of the National Institutes of Health extramural programs, are directly involved in the administration of the research and training grant programs of the respective Institutes. To a large extent the Branch exercises considerable influence upon virtually every aspect of administration (exclusive of scientific consideration) of the Institutes' grant programs, and of necessity and by request extends its operations to servicing other Bureaus of the Public Health Service and to the Office of Vocational Rehabilitation.

Functions

Essentially, the Branch facilitates the administration of the National Institutes of Health and companion agency grants programs in seven principal ways:

(1) It offers leadership in policy development and interpretation

(2) It coordinates and oversees most of the fiscal management policies and requirements applicable to grants

(3) It provides the internal procedures, and the mechanism for implementing payments and to a limited degree, control of grant funds through verification, detail recording and reporting analysis

(4) It is one of the instruments by which the Institutes execute their financial plans by reason of its role in the area of fiscal policy

(5) It attests to the legality and propriety of expenditures made by grantees from grant funds

(6) It serves as a sounding board for over 1000 grantee institutions on administrative matters

(7) It speaks for the National Institutes of Health on inter-governmental committees and before University associations on matters of mutual interest in the administration of grants programs

1960 Activity

The volume and variety of problems encountered by the Branch in its daily operations, through correspondence, telephone communication and personal contact with the Institutes, other Public Health Service Bureaus, the Office of VocationalRehabilitation and the grantees does not lend itself to a meaningful statistical measurement. It can, however, be stated that the work load is accelerating at staggering proportions as evidenced by volume of mail, calls, and transactions involving payments, recording and reporting for which the Branch is responsible. The audit program alone is seriously backlogged primarily due to inability to obtain and retain audit staff. Six thousand three hundred fifty grants were audited in 1960 and it is estimated that by the close of fiscal year 1962 some 32,000 grants will be subject to audit. Thus, the audit program is running several years behind schedule. The Branch developed and participated in the development and implementation of revisions in policy pertaining to (1) title to equipment purchases from grant funds, (2) carry-over balances in training grants, (3) procedures for Primate Centers, (4) revision in payment procedures to reduce cash balances in grantee institutions, (5) tax status of individual grantees, (6) refunds on grants amounting to less than one dollar, (7) salary policies on research grants, (8) policies on alterations and renovations, (9) fringe benefits for trainees and others of equal importance. In addition, the Branch has had increasing responsibilities involving relationships with Congressional staff and repre-

sentatives of the General Accounting Office on matters pertaining to the administration of the National Institutes of Health grants programs.

Forecast for the Future

Accelerated funding of the Public Health Service and Office of Vocational Rehabilitation grant programs in which appropriations in the last five years have increased over 400% has resulted in a mushrooming workload which strikes the Grants Management Branch with explosive force, taxing staff and facilities beyond capacity. But expanding workload is not the only factor affecting the posture of the Branch, since inherent in rapid growth is the multiplication of administrative problems in continuing programs as they widen in scope, and the complexities of handling new problems as they arise in program areas yet untouched administratively, as well as expanding relationships with individual grantees and the many institutions with whom business is conducted daily in administering the grants programs. Hence, the Grants Management Branch is obliged to handle a substantially increased administrative workload which accompanies the funds to finance the expanding extramural programs of the National Institutes of Health.

The advent of new grant programs providing for clinical research centers and the Institutional-type grants which have been authorized, impose upon the Branch additional administrative tasks, and add to the responsibilities involved in fiscal management of these new grant programs.

Accordingly, steps are being taken to strengthen the Grants Management activity through a realignment of functions by consolidating within the Branch all of the Division's functions related to financial management of grants, and the elevation of grade structure will enable it to secure capable staff to keep abreast of the rapidly expanding workload, and perform with a degree of proficiency essential to maximum operating efficiency. This should increase the total effectiveness of the fiscal administration of grants through:

(1) the further development of essential fiscal policies and procedure;

(2) improvement in internal controls and better coordination of the several grants programs;

(3) the expansion of the scope of the audit program to ensure that every proper safeguard is employed to protect the investment of the Federal Government in the National Institutes of Health grant programs; and

(4) extension of services to the granting Institutes and to the recipients of grants

Health Research Facilities Branch

The Health Research Facilities program, which provides grants for construction and/or equipping facilities for research in the sciences related to health, is administered by the Division of Research Grants.

Grants

Appropriations of $150 million have been made for the first five program years -- fiscal years 1957 through 1961. From these appropriated funds, 738 grants have been awarded to 317 institutions in 47 States, District of Columbia and Puerto Rico, totaling $144,774,290. In addition six grants, in the amount of $3,587,358, have been recommended for approval from fiscal year 1961 funds and 42 grants, totaling $11,924,851, from fiscal year 1962 funds [illegible]en available. Eighty new, supplemental and deferred applications requesting $8,389,179, now await recommendation by the National Advisory Council, and 94 letters of intent to submit applications for $33,632,870 now are on record.

Meetings

National Advisory Council meetings were held in March and June, 1960, and a meeting is scheduled for November 7-9. The first Council meeting of 1961 is scheduled for March.

Totals

As of October 1, 1960 some 212 research facilities have been completed and are in use, representing a Federal expenditure of $28.6 million and a total construction cost of over 139 million dollars.

Statistics and Analysis Branch

The general statements of objectives as set forth in the annual report for 1959 (dated 12/1/59) are altered only in the separation of the Research Information Section from the Branch when it was administratively returned to the Office of the Chief of the Division. Progress of the Branch in pursuit of these objectives during 1960 has been steady, although achieved despite unsteady progress in solving space, personnel and facilities problems.

Major actions during the year are recounted here under the three administrative units of the Branch:

Statistical Processing Section

Reorganization of the activities of this Section to achieve its expanded functions was firmly initiated in February with the appointment of Mr. Steve Remias as Chief of the Section. Staffing to implement a redesign of activities proceeded immediately but was only partially complete before a personnel ceiling interrupted essential new appointments until a week or two ago. Scarcity of project planning and programmer personnel, now lacking as immediate assistants to Mr. Remias, has created an acute staffing problem, intensifying regret over lost opportunities during the midyear hiatus on appointments.

A complete redesign of the punched card system for storage of information on grants and awards has been in course of development for many months. The new system will remove the inefficiencies imposed by crowding on a single card while greatly expanding the amount of information incorporated into the system. Thus, pending transfer to electronic data processing equipment, at least 8 cards will be utilized for information on research grants to replace the single card previously depended upon. Three cards will be used to upbuild information on all Fellows, and in a new undertaking a compact single card is envisaged to store uniformly for all Institutes a common core of coded information on all trainees appointed by grantee institutions on their training grants. Statistical information on construction grants for Health Research Facilities is also being incorporated into an expanded deck to meet the needs of this program.

The demands on specialized personnel and machines to cope adequately with this volume of information in coding, storage, retrieval and analysis operations are not only great in themselves but call for close coordination of processes extending into the machine operations. A plan has been developed to test the adequacy of continued utilization of central processing services on a new level of collaborative organization. The outcome of this test as an alternative to operation of a separate data processing facility is awaited with keen interest by the Branch as it strives to meet needs beyond the span of past experience.

Special requests to the Branch for statistical summaries and informational listings are frequently assigned wholly or in part to the Statistical Processing Section. These add considerably to their burden of routine operations leading to regularly recurring reports. The expanding national interest in supporting medical research and securing the benefits of its findings has brought with it a substantial increase in the number and scope of those special productions as well as in the detail with which information is sought. A presidential election year characterized by a majority of the major aspirants coming directly from the Senate has meant an accentuated increase in these special requests. The load on the Statistical Processing Section has accordingly expanded faster than the extramural programs have grown. Yet all special demands have been met with gratifying promptness, the annual publications of grants and awards are being produced without serious lag behind projected or previous record dates. Part I appeared on September 23 and Part II on October 20.

Design and Analysis Section

The advance, early in the year, of Dr. Fay Hemphill to the position of Assistant Chief of the Division, in charge of Training, has brought some restructuring of this Section. In assuming its direction, Dr. Deward E. Waggoner has undertaken an expanded program of special study activities which had previously been expected to be developed in the Office of the Chief of the Branch. Staffing of the Section had only reached 10 persons when the ceiling in March suspended this essential activity, but it has now been resumed to attain an immediate goal of 17 persons all unusually qualified in statistical and supporting operations.

As a sequel to development of a new PHS 2271 form giving desired biographical and fiscal data uniformly for all training programs of the separate Institutes and Divisions, the staff of the Branch has now completed abstracting all available corresponding data on old 2271 forms as filed in the offices of the respective Grants Branch Chiefs. These have been coded and are being punched on IBM cards for complete statistical analysis of the characteristics of this growing number of NIH extramural program beneficiaries. Although these records vary considerably in completeness, the analysis will undoubtedly be of great value (a) in helping to fill a past void, and (b) in providing invaluable experience for designing processing procedures under the new uniform system.

The Section has also carried prime responsibility for a comprehensive special study of all initial and repeat grantees from fiscal year 1960 extramural research funds. An interim report was issued early this summer to supplement the report of Mr. George Payne on his retrospective study of initial grantees for the fiscal years 1950, 1954 and 1958. Another interim report of almost complete coverage of both the analyses anticipated and the grantees studied was made available in November of this year. The final report will probably be available before the end of December. This unique study is providing a wealth of information in an area that had not previously been explored.

Additional special studies already initiated by this small but very industrious staff include the following temporary titles:

1. Analysis of the scientific and clinical manpower engaged on NIH research grants. (Based on applications and progress reports.)

2. The scope of support of other sponsors contributing to research projects approved by NIH, (based on applications.)

3. A differential study of approved and disapproved applications for research grants

4. The impact of research grants on training of scientific personnel (Based on applications and progress reports.)

In order to complete these studies, all applications for research grants are now being scrutinized to secure the necessary data.

Office of the Branch Chief

Under direction from this office, a universally applicable and indefinitely extensible classification scheme for medical knowledge is being sought through original research. This is essential to enable information on the coverage of sponsored investigations to be built suitably into the data storage system. When such a classification is available, it will also make feasible development of a biographical file of all NIH consultants to include detail of professional specialties. This may be combined with others on scientific manpower and stored on magnetic tape for computer searching in a large array

of desirable analytical and accounting studies of highly qualified personnel in the health specialties and their basic sciences.

A supplement to the "Grants and Awards" publications for fiscal years 1959 and 1960 is in course of preparation. It did not prove possible to complete satisfactorily an anticipated Part III to the 1959 series at an early enough date for publication. Plans have therefore been redesigned to allow for production of two separate documents in fiscal year 1960. The first of these will continue the Supplement series initiated with the fiscal year 1958 publication. This will expand the type of data previously presented and reorganize these data for greater utility in a comparative arrangement for two consecutive years.

A historical resume of the extramural programs of NIH is also well advanced, and its publication in the current fiscal year is anticipated. This volume will present a composite picture of the growth of NIH appropriations and development of the extramural programs from their inception to the present time. It also briefly traces the origin and development of the National Institutes of Health from 1887 to its present status as the principal research arm of the Public Health Service.

The Chief of the Branch also functions as NIH Reports Officer. A number of new or revised forms has been developed cooperatively with the originators before submission to the Bureau of the Budget for clearance.

The DRG budget provides for a full-time specialist to cover the problem of form design in order to achieve with maximum simplicity and brevity the objectives for which each form is created. This can be achieved only by continuing a comprehensive study of these forms from their origin to the statistical analysis of the results produced. Such a specialist is, however, still being sought to fill this rather unique position.

Research Fellowships Review Branch

The number of fellowship applications received by the Branch during calendar year 1960 was significantly higher than in previous years -- an estimated 4,000. This is in contrast to a total of 2,109 received in 1958 and 2,848 in 1959. In the first nine months alone of 1960, 2,869 applications were received.

Review Panel Changes

Up to the present time, the review and evaluation of regular fellowships applications have been the responsibilities of panels composed chiefly of NIH research personnel. The Branch is now engaged in the establishment of panels of outside specialists who will be more familiar with the academic world. These newly constituted panels of the Central Qualifications Board will meet for the first time before the end of the present calendar year. The number of panels has been increased to ten with the establishment of one in the Mental Health area.

Analysis and Evaluation Section

The Analysis and Evaluation Section established late in 1959 is now compiling reports for comparison with the various training grant programs on twenty-three identical items and on an additional twenty-eight items relevant only to the regular fellowships programs. A study reported to the National Advisory Cancer Council on the mobility trends of fellows between Institute of support and subsequent institute-related field of employment made on the basis of the returns in the 1957 follow-up showed that 36 percent of the former NCI fellows remained in an institute-related field of employment. A fourth follow-up of approximately 5,500 former fellows is planned for late November 1960. The new follow-up is more detailed and comprehensive than previous ones.

Senior Research Fellowships

The Senior Research Fellowship Grants Program has been expanded to include clinical as well as basic science areas and will no longer be strictly a DGMS offering. Since these grants will now be available from all Institutes, the Research Fellowships Review Branch will be responsible for many activities prior to assigning them to an Institute or DGMS where they will be reviewed and awarded. Special Fellowship Grants will also be available from most Institutes and here too this Branch will be responsible for the development of policies, rules and procedures. The activities of the Branch in these two programs will be comparable to those of the Training Grants Section.

Internal Operations Branch

The Internal Operations Branch provides a variety of administrative, service and housekeeping functions for Division personnel, as well as certain central services for the extramural programs of other Divisions and Institutes.

The revised organization of the Branch is as follows:

Office of the Chief - provides overall supervision of all Branch activities and maintains liaison with other Divisions and Institutes.

Office Services Section - This section performs a variety of functions and duties, particularly those concerned with procurement, property, supply, and documents relating to these activities. In addition, this section has just inaugurated a Distribution Unit to assure more accurate and more thorough distribution of the vast quantity of papers, documents, brochures, pamphlets, etc. that are either produced or received by the Division.

Special Services Section - This Section is primarily concerned with providing special services, such as flexowriter, general typing, extra clerical and typing help on occasion, and controlled supervision of the various types of office duplicating machines located throughout the Division (Spirit duplicating, Thermofax, Masterfax, GBS Punch and Binding machines.) In addition, this section is initiating a complete addressograph operation.

Mail and File Section - This section expedites the tremendous flow of mail coming in to the Division each day. Since the conversion to the open shelf files about 18 months ago, the volume of records maintained on these shelves has doubled, due primarily to the heavy influx of audit files on approved grants coming in from the institutions. The linear footage of shelving has been increased by about 45%,whichso far has been adequate to handle the workload.

Travel Section - This section recently increased its staff to accommodate the additional workload reflecting the entire Division's growth. A recent innovation in handling the payment of fees, and reimbursement for travel costs, shows excellent promise of expediting this phase of the operations.

Duplicating Section - The addition of a Duplication Officer has done much to help the shop establish new procedures and achieve the goal of complete automation and systemization. Late in the past fiscal year, and early in this one, the shop acquired approximately $137,000 worth of new equipment: 6 fully automated offset presses, one new 12 station collator, one new 50-bin collator, one new 5-headed paper drill, a Copyflo continuous printer for making offset masters, plus other miscellaneous equipment to modernize the shop. Consequently, the Division no longer needed the satellite shop in the Robin Building. An open-house demonstration was held September 14, to acquaint all NIH personnel with the new facilities. About 500 persons attended the demonstration. New procedures now being worked out should make it possible to eliminate many of the time consuming operations formerly done in the shop.

During the past year, some of the functions of the Branch were transferred to the Office of the Chief, DRG, or to other Branches. They are: personnel administration, recruitment, time and leave, to the Office of the Chief, DRG; Budget Examiner, to the Office of the Chief, DRG; Grants Finances Section, composed of: the Grant History Card Unit, the Grants Payment Unit and the Audit Reports Unit, to the Grants Management Branch.

The Study Sections

In addition to their responsibility for conducting the technical review and appraisal of research applications and making recommendations to the Advisory Councils, the Division's 36 study sections also develop and encourage research in neglected areas of the health, medical, or related sciences.

During the past year, the study sections planned and programmed a variety of scientific conferences; sponsored the publication of proceedings of selected symposia; conducted evaluations of their individual programs and programmed in new areas; and engaged in a wide variety of other related activities.

A number of the study sections are in the process of being reorganized and redirected in order to strengthen various areas of research grant review. Some of the significant activities within the study sections during 1960 follow.

Behavioral Sciences Study Section

Since its establishment in January 1960, the Behavioral Sciences Study Section has reviewed 216 applications covering such diversified areas as the epidemiology of mental disorders, cognitive processes and attitude formation, language and communication, cross-cultural psychological and anthropological studies, social structure and small-group behavior, and the evaluation of teaching methods and curriculum outcomes. With the addition of three prospective new members, the Study Section will achieve maximum strength for the coming year, when an increase in the number of applications falling within its broad purview is expected.

During the first year of its operation, the Study Section was of necessity unable to initiate any of its programing interests. However, a number of conferences have been suggested, and it is anticipated that with stablization of its membership and firm establishment of its methods of review operation, the Study Section will soon be active in sponsoring conferences and symposia on such topics as the development of standards for cross-cultural research, the development of standards for scientifically oriented investigations of delinquency, alcoholism, and narcotic addiction, and the development of a method for assessing research productivity, with the potential of deriving predictive indices useful in the evaluation of research grant applications.

These are, of course, only suggested areas of activity. It is anticipated that ad hoc committees will be set up for the purpose of detailed planning of any conferences or symposia to be held during the coming year. It may be that other areas prove more demanding of attention than those noted above; for example, reports of recent developments in the Soviet Union involving the planned separation of children from parents.

Mental Health Study Section

During the calendar year 1960, the Mental Health Study Section reviewed 248 research grant applications in the fields of clinical psychology, clinical psychiatry, personality, and developmental processes. Of these, 89 were approved, 156 disapproved, and 3 deferred.

One-half day during the September meeting of the Study Section was devoted to a discussion of the Criteria for the Evaluation of Clinical Research. The discussion soon broadened, however, to include problems of research design in areas such as anthropology and sociology, as well as clinical psychology and psychiatry, where the research problem may be somewhat undefined or the structure of the research situation may be unfamiliar. These problems of design arise in surveys, natural history research, naturalistic observation, and phenomenology, in addition to the fields mentioned above.

The Study Section formed a sub-committee to study these problems with a view toward sponsoring a conference on them.

Experimental Psychology Study Section

The Experimental Psychology Study Section completed its first three meetings during calendar year 1960. A total of 184 applications was reviewed, of which 70% were given favorable recommendations.

At the September 1960 meeting, the Study Section formed a sub-committee to consider research on the problem of learning without awareness; this group is to present a plan for a small working conference on this subject, along the lines of the Skytop meeting organized in 1959 by the original Behavioral Sciences Study Section. The Study Section felt that possibly such a conference could have a salutary effect on the quality and sophistication of proposals on the subject of learning without awareness. In addition, the hope was expressed the proposed meeting may clarify certain currently controversial issues, as to the nature of the expectancies verbalized during the acquisition of a conditioned autonomic response.

Psychopharmacology Study Section

During its first full calendar year the Psychopharmacology Study Section reviewed one hundred and forty applications. During the three meetings involved the approval rate varied from thirty-five percent to forty-five percent; on an overall basis fifty-six applications were approved, a rate of forty percent.

The Study Section has been concerned about the quality of applications received in this field. On its agenda for the first meeting during calendar year 1961 will be a discussion dealing with the problem of encouraging investigators of proven as well as those of high potential ability to apply for NIH support; and to discuss other possible ways of stimulating increased research efforts in this relatively new field, while at the same time maintaining high critical standards.

Nutrition Study Section

The Nutrition Study Section entered its second year of operation and at the time of this reporting its review load is increasing significantly. Notwithstanding this increase in review responsibilities, the Study Section has had a broad program of interest in the field of nutrition. It has co-sponsored five conferences, three of which have already taken place:

1. Problems of Nutrition Appraisal of Man. April 1960. At Annual Meeting of Federation of American Societies for Experimental Biology, Chicago, Ill.
2. Interaction of Mineral Elements in Nutrition and Metabolism. (H-5104) April 1960. At Annual Meeting of Federation of American Societies for Experimental Biology, Chicago, Ill.
3. Conference on Protein Needs (A-3844) August 21-24, 1960, Washington, D. C.
4. Role of State Health Departments in Nutrition Research (A-4726) Planned for April 1961, Arden House, Harriman, New York

5. Marine Food Resources and World Nutrition (RG-8301)
Planned for September 1961, Washington, D. C.

Readily evident in the nature of these conferences is the interest of the Study Section in the experimental aspects involving population groups here and abroad. In very large part, the interest of the Study Section in international nutrition problems stems from the fact that it is directly representing the interests of the nutrition field.

Continued close liaison has been maintained with the Food and Nutrition Board of the National Academy of Sciences, the Interdepartmental Committee on Nutrition for National Defense, and agencies of the United Nations. Several of the Study Section members have received recent appointments to scientific advisory committees of these various groups.

There appears to be a renewed interest in nutrition which is about equally divided between clinical and laboratory type investigations. The recent formation of a clinical group within the American Institute of Nutrition would appear to signal even greater emphasis for the future on problems of human nutrition. No doubt, many of these investigations will take place abroad where living conditions of various population groups afford excellent study material.

In general, it may be said that nutrition is again coming very much into its own, with less diffuse overlapping in areas reviewed by other Study Sections.

Hematology Study Section

In addition to a moderately heavy load involving review of applications for research grants in the field of hematology, The Hematology Study Section, under grants from the National Heart Institute, sponsored two conferences on the subject of thrombolytic agents. One was entitled "Conference on Thrombolytic Agents" and was held in Chicago, Illinois, on April 8 and 9, 1960. It was attended by approximately one hundred twelve investigators. The proceedings have been published and have been made available for general distribution.

The Study Section cosponsored on September 18-21, 1960, with the International Committee for the Standardization of Nomenclature of Blood Clotting Factors, a conference on thrombolytic agents at Princeton, New Jersey. This was an international meeting to discuss both the basic science and clinical aspects of fibrinolysis. The meeting was attended by approximately one hundred thirty-five investigators.

Environmental Sciences and Engineering Study Section

The Environmental Sciences and Engineering Study Section, formerly the Sanitary Engineering and Occupational Health Study Section, was renamed in September.

In addition to its continuing responsibilities for the review of research grant applications lying within its disciplinary area, the Study Section undertook to stimulate research through sponsorship of a two-day conference (Sept. 8-9) on Physiological Aspects of Water Quality, held in Washington, D. C.

Citing the need for an appraisal of the present state of knowledge about the physiological effects of certain chemical constituents of water, the conferees focused their attention on the question of what research can and should be undertaken in the field with a view toward creating a healthier environment.

The meeting of 63 participants included present members and several former members of the Study Section, and brought together physiologists, toxicologists, chemists, biologists, statisticians and sanitary engineers.

Proceedings of the conference will be published, and will contain the presentations of principal speakers, a summary of the general discussion, and resulting suggestions for future research.

Calendar year 1960 activities of the Study Section included planning for a conference to be held May 10-11, 1961, also in Washington, on Epidemiologic Opportunities in Occupational Health. The Division of Occupational Health, Bureau of State Services, collaborated with the Study Section in developing the program. This conference will consider the present status of information about health problems existing in employed populations and possibly related to the environmental conditions of occupation. Conferees will explore research possibilities, and ways of stimulating research in neglected areas and overcoming obstacles to medical research in industry. Proceedings will be published.

Virology and Rickettsiology Study Section

One of the outcomes of the Virology and Rickettsiology Study Section's interest in stimulating more research in the area of viruses and cancer was the symposium, "Phenomena of the Tumor Viruses," supported by a grant to Dr. Joseph W. Beard, the general chairman. The symposium, held in New York City on March 25,26, 1960, was attended by more than 300 investigators from this country and abroad. The proceedings have been published as the National Cancer Institute Monograph No. 4. (376 pp.)

While the bulk of the applications examined at the three meetings were concerned maily with basic aspects of viral replication, nucleic acids and host-parasite relationships, increasing proportions of applications have been noted in the areas of plant, tumor, respiratory and arthropod-borne viruses. Increasingly, the modern virologist, like other biologists, is concerned with processes at the macro- and molecular level. This receives impetus from the exciting findings in the area of nucleic acid metabolism and function as related to viral replication as well as to cancer.

Because of the confusion created by the continued isolation of new viruses concerned with respiratory diseases, the Study Section is planning to discuss the needs for a good basic symposium on this subject.

Human Embryology and Development Study Section

In January 1960, the Human Embryology and Development Study Section held a Special Session to which all the former members of the Study Section and all the members of Embryology and Development Training Committee of DGMS were invited. The purpose of the meeting -- held immediately after the regular business session -- was to review the Study Section activities for the first 5 years of its existence.

After the meeting it became apparent that it would be inadvisable for the Study Section to continue to have responsibility for the review of applications dealing with the NINDB Cerebral Palsy Program. The responsibility for the review of such applications was transferred to the Perinatal Research Committee set up for this purpose within the NINDB. Several members of the Study Section who previously served on the ad hoc Cerebral Palsy Review Committee left the Study Section to join the newly created Perinatal Research Committee.

At its September meeting the Study Section decided to plan a symposium or conference to be held sometime in 1961 and which would be sponsored jointly with the Association for the Aid of Crippled Children. The Chairman appointed a subcommittee to prepare a detailed plan for this purpose and report back at the next meeting.

Pathology Study Section

During 1960 the Pathology Study Section reviewed 444 applications, recommending approval for 326, or 73%. Project site visits were made in connection with 64 requests.

In order to further familiarize the Study Section with new developments in field related to Pathology, a Workshop on Germ-Free Life research was held at the National Institutes of Health in connection with the January meeting. The Workshop was arranged by Dr. Walter L. Newton of the NIAID and included representatives of other laboratories at the NIH and at Walter Reed. The guest speaker was Dr. Helmut Gordon of the LOBUND Institute, Notre Dame, Indiana. Members of the Pathology Training Committee, DGMS, and of the Intersociety Committee for Research Potential in Pathology attended the meeting as guests of the Study Section.

This year saw the implementation of several new projects previously considered by the Study Section. A survey of factors affecting recruitment, training and development of research interests of pathologists, was initiated with the help of funds provided through research grant RG-8168. An exhibit, stressing recent developments in research and the role of the Public Health Service and other agencies in the support at private and public institutions, will be constructed with funds made available in research grant 2G-313 to the Intersociety Committee for Research Potential in Pathology. A conference, "Horizons in Neuropathology," is planned for the fall of 1961 with the aid of a grant from the National Institute of Neurological Diseases and Blindness, B-3187. This will be a teaching conference, aimed at trainees in neuropathology and young pathologists who may be interested in entering the field.

Arrangements are in the making for Workshops in Radiation Pathology and Quantitative Histology. The Study Section also agreed to sponsor a second Symposium on Nutritional Disease, providing that it was an open teaching symposium and not a closed meeting.

Surgery Study Section

During 1960 the Surgery Study Section reviewed a total of 325 applications of which 225 were recommended for approval, 83 for disapproval and 17 were for deferral. The total number of applications reviewed in 1960 represents an increase of more than 16% over the number reviewed in 1959. Eight project site visits were made during the year by Study Section members.

A pamphlet entitled "The Care of the Dog in Medical Research," originally developed by the Section, is undergoing revision and will be published as an official PHS publication. This will be the third edition of this pamphlet.

In view of the large amount of research being supported by grants from NIH and other granting agencies on the problem of prosthetic heart valves, and the need for an exchange of ideas and results by the investigators in order to avoid needless duplication of effort in resolving problems in this area, the Section sponsored, with grant support from the National Heart Institute, a Conference on Prosthetic Valves for Cardiac Surgery. This conference was held on September 9-10, 1960 at the Edgewater Beach Hotel, Chicago, Illinois, and was attended by 251 individuals most of whom are actively engaged in research related to the use of prosthetics in cardiac surgery. Participants and guests represented industry as well as university, government and private medical centers. The foreign countries represented were: Argentina, Canada, England, France, Puerto Rico and Sweden. The formal papers presented, together with the discussion, are being prepared for publication in the form of a bound text book by the Charles C. Thomas Company. This book is expected to be available about March 1, 1961.

Advisory Panel on Accident Prevention

The Advisory Panel on Accident Prevention was formed to provide a continuing body of consultants from a number of disciplines, who would serve on an ad hoc basis to review applications for research grants aimed at the prevention of accidents and the reduction of injury resulting from accidents. In addition to the review of applications, the Panel provides a multidisciplinary advisory group with a real interest in the problems concerned with research in this area, a willingness to focus on these problems, to follow the progress of research in the field, to point out neglected areas, and to provide encouragement of good research in these areas.

Of the 31 grants (totaling $4,345,155) that have been made in this area since September 1958, when the Panel began to review applications: 20 are concerned with traffic accidents, 2 with aviation accidents, 5 with home and farm accidents, 1 with effects of acceleration on the human skeleton, 1 with the design of protective helmets for athletic and industrial use, and 2 for the preparation of bibliographies. Of the 20 research projects concerned with traffic accidents: 5 are concerned with accident inducing character-

istics of the automobile and safety devices; 8 are concerned with psychological or sociological characteristics of the driver; 5 are concerned with drivers' training or the re-education of accident repeaters; 1 is an intensive investigation of causes of fatal accidents, and 1 is a study of the type and extent of injuries sustained in traffic accidents.

Most of these studies have not been underway long enough to be able to show significant results. Some, however, are continuations of projects that have been active long enough to show results and have already had an impact upon the design of automobiles and aeroplanes and have attracted the attention of legislators at both State and national level. In this category fall:

RG-4367, the Cornell Crash Injury Research Project
RG-7050, Automobile Collision Injury Experiments at the University of California at Los Angeles
RG-6506, Aviation Crash Injury Research of Flight Safety Foundation

One project, RG-6094, a study entitled "Impact Attenuation in Protection against Concussion" has recently received very favorable comment at the London meeting of the International Organization for Standardization, which is an outgrowth of the United Nations Standards Coordinating Committee.

In fiscal year 1960, there were 27 grants for research aimed at accident prevention, amounting to $1,232,985.

Nursing Research Study Section

For the purpose of determining areas of nursing research which may be troublesome or unusually active or slow, a statistical report was made of Study Section actions for the period April 1957-January 1960. This report showed percentages of applications and amounts of support approved and reviewed, approval rate and priority scores assigned, and applications disapproved and reason for approval, by type of projects. The Study Section anticipates making periodic overall surveys of both approved and disapproved applications.

Invitations have been extended to and accepted by the two major national nursing organizations to discuss with the Study Section at its January 1961 meeting their views as to research needs in nursing and their plans for conducting research during the next decade. At the April 1961 meeting a similar discussion will be held with nurses from Federal agencies. Early in 1960, the Study Section invited and received reports on the progress of programs for training nurses for research, and on trends and objectives of research in public health fields. Research to determine the effectiveness of current health protection activities, and research on the administrative process were focal points in the discussion.

The Study Section reviewed the use of the participant observation method of data collection in applications received during a two and one-half year period. The purpose of the review was to suggest a framework for considering some of the questions raised as a result of the rather widespread misunder-

standing of the nature of the method and the conditions which its use presupposes. The feasibility of initiative being taken by the Study Section in training nurses in methods of participant observation has had preliminary discussion and continues under consideration.

The Study Section continued to conern itself with evaluating the outcomes of nursing research grants, as a measure of its effectiveness in reviewing applications. In this connection, thought has been given to taking a "second look" at projects after a year or two of operation to see if the investigator really has a new idea that will challenge other people. One problem has been the lack of a common understanding as to what is being talked about when the term "nursing research" is used. An attempt to clarify this concept will be made at a future meeting.

The Study Section approved plans for its participation in the Division's study of the epidemiology of disapprovals. At its September 1960 meeting, in addition to assigning an overall rating to approved applications, it rated approved and disapproved applications according to the four elements of problem, plan, man, and other. It is planned to continue this procedure, at least for a few meetings.

Human Ecology Study Section

The Human Ecology Study Section held its first meeting in September 1960. The Section is primarily concerned with research grant applications (1) which propose to measure or compare the presence, nature, and distribution of health or disease in large populations in relation to factors or stimuli which influence such distributions and (2) applications which propose to develop or refine methodologic techniques useful in the prosecution of such commodity studies.

In line with the Study Section's responsibility to encourage and stimulate research in neglected areas, the Section sponsored a workshop conference on Health Studies of Human Populations held on November 13-16, 1960 at the University of Pittsburgh. The Conference was attended by 60 researchers from this country and abroad who were charged with the establishment of guidelines for use by investigators contemplating projects in this field and by NIH Study Sections and Councils in their evaluation of project applications.

The Conference focussed primarily on twelve current examples of community research projects and considered such factors as the size and character of the population studies in relation to the objectives, methods of collecting and analyzing data, and the administration, staffing, and financing of such projects. It is hoped that a report of the Conference proceedings will be available by mid-1961.

Neurological Field Investigations Study Section

The Neurological Field Investigations Study Section, while reviewing a relatively small number of applications, has had a programming function to carry out in behalf of the National Institute of Neurological Diseases and Blindness. In this connection the Study Section initiated a conference held

in March to explore the research potentialities of chronic disease hospitals.

The Study Section set up a subcommittee to explore promising research approaches to the problem of uveitis. Three meetings of the Committee took place in 1960. The Study Section also sponsored and organized a workshop conference on diabetic retinopathy in Haddonfield, New Jersey on May 1 and 2, 1960. There were approximately thirty participants representing various disciplines in the discussion of the research approaches to this important problem.

Cardiovascular Study Section

During calendar year 1960 the Cardiovascular Study Section reviewed 341 applications. Of these, 204 (totaling over ten million dollars) were recommended for approval and 137 for disapproval. Members of the Study Section visited 17 medical institutions during the course of the year.

A group discussion on small blood vessels was held in Bethesda in September 1960. Ten guests, all outstanding investigators engaged in various phases of this work, were invited from medical centers throughout the United States. The extent of our present knowledge on the structure and function of small blood vessels was thoroughly debated. Several areas requiring more work in this field were outlined. It is expected that this type of informal exchange will provide a quick and stimulating flow of information between the several disciplines concerned with the same overall subject as well as furnishing the most up to date bases for study section appraisal of applications. A summary of the most pertinent aspects of the discussion will be made available to other investigators. Additional conferences are planned for the future.

Tropical Medicine and Parasitology Study Section

The membership of the Tropical Medicine and Parasitology Study Section is composed of specialists who hold medical, veterinary, and research degrees, who have a wide scope of interests and competence encompassing all disciplines in medicine in the tropics, and who are located in the tropics or in areas where research in medicine in the tropics is emphasized. The study section has enhanced its efforts to encourage better oriented, more inclusive interdisciplinary research in all fields of tropical (geographical) medicine.

The Fourth Conference on Research Needs in Tropical Medicine was held at the School of Medicine, Louisiana State University, in New Orleans on April 29-30, 1960. More than 200 authorities from the United States and 17 foreign countries were invited to participate in the four sessions. The subjects of the sessions and the coordinators were: Tropical or Geographical Medicine, Dr. William W. Frye; The Impact of Modern Instrumentation on Medicine in the Tropics, Dr. Theodor von Brand; and two sessions on Critical Problems Needing Investigation in Some Fields of Medicine in the Tropics, Dr. Robert Dyar and Dr. Justin Andrews. Following the conference, the study section recommended that University Centers for Research in Tropical Medicine be established in the United States with each Center having complementary facilities in overseas locations. When such American Centers and overseas facilities are available, it will be possible to undertake the expanded, interdisciplinary research as recommended by the conferees and cited in the Proceed-

ings of the Conference. Copies of the Proceedings are available in the Office of the Executive Secretary of the Tropical Medicine and Parasitology Study Section.

The study section encouraged the compilation and publication of a booklet, "100 Problems in World Medicine" as a means of better orienting research in the area and suggesting possible research projects for beginning investigators.

During this year the number of applications reviewed by the Tropical Medicine and Parasitology Study Section has doubled. The scope of subjects has been broadened to include the zoonoses and studies in nutrition, ecology, and pathology as related to tropical medicine in addition to expanded studies in infectious diseases.

The study section plans to sponsor the following conferences during the next four years:

1. Second Conference on Research Needs in Bat Rabies (Co-sponsored with the Virology and Rickettsiology Study Section) (1962);
2. Symposium on Research Needs in Toxicology (Co-sponsored with the Toxicology Study Section) (1963);
3. The Culture of Organisms on Defined Media (1964); and
4. Fifth Conference on Research Needs in Tropical Medicine (1965)

Metabolism Study Section

The Metabolism Study Section activities during 1960 reflected continued interest in the stimulation of research on metabolic abnormalities in various disease states.

In January the Study Section conducted and Insulin Bioassay Seminar, held in Los Angeles in conjunction with the American Diabetes Association Post-Graduate Course. About 40 experts in techniques of analysis for insulin and insulin-like activity found this an excellent opportunity to exchange views comparing the several methods for insulin assay. Dr. A. B. Hastings, of Scripps Clinic, and former Metabolism Study Section Chairman Dr. P. H. Forsham led in the formulation of the program and the conduct of the sessions, the proceedings of which were summarized in the July-August, 1960 issue of the journal "Diabetes."

Study Section support of meritorious research efforts abroad included a favorable recommendation on an application from a young research worker in Korea. This provided part of the background for a Voice of America broadcast to that country, in which the Executive Secretary participated.

The Metabolism Study Section gave particular emphasis to programs in cardiovascular research. Earlier, the members had expressed their interest in the stimulation of research in the chemistry and metabolism of lipids. During the year a close working relationship was developed between the Study Section and the National Heart Institute, towards implementation of a plan for the advancement of methodology in lipid research. Aware of deficiencies in the supply

of certain lipid compounds needed by research workers, the National Advisory Heart Council recommended the provision of funds to enable distribution of such substances to qualified investigators. A Lipid Advisory Committee was selected, consisting of experts in lipid biochemistry. These act as a subcommittee of the Study Section in advising the Division of Research Grants and the National Heart Institute on technical phases of this program, with the Executive Secretary acting as project officer. The program has already made important contributions to the gas chromatography field, and steps are now being taken to implement first stages in the distribution process.

The Study Section also emphasized its desire to see further research to evaluate effects of various metabolic influences on coronary heart disease. Particular attention was suggested toward such factors as diet, exercise, emotional stress, pharmacologic agents, endocrines, genetics, and the like. The Heart Council has expressed its interest in support of efforts in these directions, and Study Section Chairman, Dr. E. H. Ahrens, Jr. has now scheduled the first meeting of a planning group of experts with interests in areas related to the problem, for preliminary discussions.

Dental Study Section

During calendar year 1960 the Dental Study Section reviewed 237 applications, of which 105 were recommended for approval, 110 for disapproval, and 22 for deferral.

The Dental Study Section inaugurated a policy of performing "generalized" site visits to institutions with especially active dental research programs. These visits are made by at least 4 or 5 Study Section members representing several specialities, and do not refer to any one research grant application. Rather, they are designed to acquaint the Study Section with the entire research program of the institution -- its aims and potential -- and to convey to the investigators the interests, responsibilities, and method of procedure of the NIH review bodies. To date, three of these visits have been made, and appear to have resulted in an improved understanding on the part of all participants. More of these visits are planned, to whatever places the Study Section believes might profit thereby with a strengthened research effort.

In connection with this policy, the Study Section has also recommended that at least one formal Study Section meeting per year be held in an area where several research institutions are located which could be contacted in the aforementioned manner. It is planned to have the Spring 1961 meeting in a large metropolitan center so that the review of grants applications can be supplemented by conferences with grantees, applicants, and officials of several institutions in the area.

A series of contacts have been made with researchers in non-dental institutions with the aim of attracting to the NIH dental research program applications for the support of studies basic to the understanding of the biochemical and physiological processes involved in the formation and maintenance of all tissues including those of the oral cavity. An encouraging degree of response has been received, especially from those people interested in calcification mechanisms.

The Dental Study Section is currently planning the sponsorship of a series of international conferences on problems important to dental research. Topics have been suggested and an order of priority will be established before definite plans and the assignment of individual responsibilities are made. The topics under consideration are as follows:

1. The biochemistry and physiology of saliva
2. Mechanisms of calcification and decalcification
3. Recent progress in clinical and research orthodontics
4. Biometry as applied to dental problems
5. Recent progress in dental materials research
6. The physiology of pain

General Medicine Study Section

In the calendar year 1960 the General Medicine Study Section reviewed 208 applications in the fields of Dermatology, Rheumatology, Gastroenterology and various other phases of Internal Medicine. A total of 120 applications, valued at nearly 7 million dollars, were recommended for approval. Eighty-eight applications requesting nearly 6 million dollars of support were not favorably recommended.

Ninety-six of the research proposals dealt with gastroenterology, including liver disease, intestinal malabsorption, colitis, gastritis, and associated clinical problems. Twenty-seven proposals were in the field of Rheumatology and 22 in Dermatology. Of the 52 applications categorized as other internal medical problems, 17 proposed clinical studies on various metabolic errors, eleven were concerned with renal disorders, 11 with diabetes, 6 with clinical endocrinology, and 7 were miscellaneous proposals.

Current trends show an increase in the number and variety of research proposals coming to the attention of the study section. To facilitate review of applications, a moderate increase in the number of consultants in the major fields will be required.

Genetics Study Section

During 1960 the Genetics Study Section reviewed a total of 160 applications for research grants, of which 73% were new applications. In addition, the Study Section is engaged in a work-study program and is carrying on specific collateral activities which it believes will contribute materially to the expansion of research in genetics, and to sound growth of medical genetics in its broad aspects. There are an outgrowth of an earlier survey of the status of genetic research and subsequent delineation of the more urgent areas in which the Study Section felt it could provide effective and realistic assistance. Major aspects of the overall program are summarized below:

1. Current Research Methodology in Genetics --- Through a series of symposia, advances in research techniques, special procedures, including information on genetic stocks, equipment sources, etc., are being summarized in three volumes entitled "Methodology in Medical Genetics." The first symposium was held May 13 and 14,

1960 in Salt Lake City and the resultant volume dealing with Methodology in Human Genetics is in press. The second conference, summarizing Methodology in Mammalian Genetics, was held September 9 and 10, 1960 in Bar Harbor, Maine, and work has just begun on preparation of the second volume. Material to be included in the third volume, Methodology in Basic Genetics, will be presented at the symposium devoted to this topic in May 3, 4, 5, 1961 at Austin, Texas. The series will be published by the University of Columbia Press, and it is expected that the volume on Human Genetics will be available at the time of the final symposium. This work constitutes a major undertaking on the part of all members of the Study Section. In addition, the cooperation of other leading geneticists both here and abroad has been secured for specific contributions to the symposia and methodology volumes. This program, including publications, is supported by the Division of General Medical Sciences, research grant No. 7097.

2. Expansion of Genetic Research --- In the interest of strengthening genetic research and the expansion of these efforts in the area of human genetics, the Study Section has considered how and where: a) new foci of research might be established; b) existing departments, laboratories, institutes, etc. might be strengthened and expanded. To this end the Study Section's activities are coordinated with genetic program development of the various institutes, through their staff and respective advisory councils. For example, at the request of the Division of General Medical Sciences an ad hoc committee representing the Genetics Study Section, DRG, and the Genetics Training Committee, DGMS, met on November 12, 1960 to define the immediate and long range needs and opportunities for expanding support in medical genetics. The resultant report includes specific recommendations, which if implemented will have a strong and far-reaching impact on the expansion of training and research in this field.

3. Genetic Literature --- A third phase of Study Section effort concerns problems of management of genetic literature, with the aim of facilitating the dissemination of research results in practical and useful forms. Informal discussions with journal editors, the publisher of Current Contents, and others have so far resulted in: a) the addition of approximately 35 U.S. and foreign genetics journals to those now included in Current Contents, to provide essentially complete coverage of current publications in the field of genetics; b) The Institute for Scientific Information has been encouraged to develop and publish a "Citation Index" for genetic literature.

4. Research Manpower in Genetics --- A study is being made of the research manpower in genetics, including the nature of training, degree-institution, present address, etc. From information

supplied by the National Science Registry and American Institute of Biological Sciences, the Study Section is compiling a directory of geneticists, and is carrying out analyses of interest to those concerned with research manpower in this field.

5. Genetic Stocks --- The Genetics Study Section assists in the continuous review and assessment of needs for genetic stocks in areas of special concern to medical genetics and the National Institutes of Health. Through Study Section representation on the national committee and the Executive Secretary, close liaison is maintained with the Genetics Society of America's "Committee for the Preservation of Genetic Stocks" to coordinate efforts on a national basis.

Toxicology Study Section

Aware of the sudden emergency of environmental toxicity as a social problem, the Toxicology Study Section co-sponsored its second symposium within a year. This study section joined with the Food Protection Committee, NRC, and the Toxicology Committee, NRC, to organize a symposium on Toxicology. It was presented at the annual meeting of the Federation of American Societies for Experimental Biology in Chicago on April 13, 1960. The program consisted of a series of talks by outstanding investigators. The subject matter reflects the social implications of the toxicities of food, drugs, cosmetics, and contaminants of food, water and air. Several papers were concerned with the recognition of Toxicology as a scientific discipline and with the training of toxicologists.

The meeting was divided into a morning session and an afternoon session. Attendance was estimated at 500 persons at each session. The papers were published as a Part II of the September 1960 issue of the Federation Proceedings. Copies were furnished to members of the various societies in the Federation. Reprints were also furnished to the collaborating groups and extra copies were obtained to be used by this study section for programming purposes.

This symposium was funded by the Division of General Medical Sciences, NIH, and by the Food Protection Committee, NRC.

Reprints of the previous symposium on Food Enzymes will be published by the Avi Publishing Company in book form. This symposium was co-sponsored by this study section and the Department of Food and Dairy Technology, Oregon State College. It was funded in part, by the Division of General Medical Sciences, NIH.

The study section intends to continue to encourage Agricultural Colleges, School of Veterinary Medicine and Schools of Public Health to explore the appropriate areas of environmental health.

The September meeting of this study section was held in San Mateo, California. The members, as a group, visited several laboratories of scientific interest to the study section. Informal discussions were mutually advantageous in that the investigators were made aware of the interests of the study

section and they were encouraged to make realistic attempts to expand their efforts in these areas.

During calendar year of 1960 this study section reviewed 75 applications and recommended 60 (80%) for approval.

Neurology Study Section

A symposium on "The Response of the Nervous System to Ionizing Radiation" was held at Northwestern University, Chicago, Illinois, on September 7, 8, and 9, under the joint sponsorship of the Neurology Study Section and Northwestern University. Several members of the Neurology Study Section participated in the 3-day program, and 300 scientists attended. This symposium was supported by a grant from the National Institute of Neurological Diseases and Blindness and the Atomic Energy Commission.

Pharmacology and Experimental Therapeutics Study Section

The Pharmacology and Experimental Therapeutics Study Section continued to review applications in the broad areas of its competence. As a result of its earlier "Symposium on Catecholamines", investigators are now studying metabolism of these compounds using approaches that combine chemical identification of the metabolites with a biological assay to better evaluate the significance of their findings. By its review the study section is stimulating more profound investigations of drugs and their action on tissues and organs.

In an attempt to lessen the workload of the study section, about 80 active grants were transferred to the new Medicinal Chemistry Study Section. These were grants primarily concerned with the synthesis of organic chemicals which were to be screened for biological effects by others. Grants and applications in which the investigator is primarily interested in the pharmacological effects of organic compounds, will continue to be reviewed by the Pharmacology and Experimental Therapeutics Study Section.

With the formation of the Toxicology Study Section, ten active grants on the mechanism of action of pesticides were transferred to this group. In spite of these transfers, this study section reviewed 288 applications during the current calendar year. Of these, 188 (65%) were recommended for approval.

The study section hopes that with a dimunition of workload, it will be able to spend more time in its cofunction, the surveillance of research in pharmacology to determine areas in which research activity should be initiated or expanded.

Endocrinology Study Section

The Endocrinology Study Section continues to receive and process requests for several steroid and pituitary hormones. It is estimated that between 300 and 400 requests are received annually.

Early in 1960 we made contacts throughout the United States for the collection of human pituitaries. The success of this program has been good and the collection is running at the rate of approximately 7,000 pituitaries per year. The human pituitaries are being processed and are at this time being furnished for treatment and experimentation in unusual cases of human disease in our own Clinical Center and other selected research laboratories.

Since human urine can also be a source of pituitary products, the Study Section has developed sources of urine which are particularly rich in these products. One source is a population of 77 castrate human males living in an institution in Winfield, Kansas. Another source is a group of over 100 postmenopausal women living in a home for retired nuns in Milwaukee, Wisconsin. The urine receives a primary processing and then is sent to research laboratories in the Mayo Foundation in Rochester, Minnesota, for further purification and study. It is hoped that these urine preparations will lead to a world-recognized National Institutes of Health standard preparation with both research and clinical value.

At the May 1960 meeting of the Endocrinology Study Section, an application was recommended to support a work conference on Neuroendocrinology. The grant was awarded through the National Institute of Neurological Diseases and Blindness and plans for the conference are now almost complete. The meeting is scheduled to take place in Miami, Florida, December 1961.

Approximately 350 applications for grants in aid of research are reviewed annually with resultant recommendations being made to respective councils.

Serial No. DRS-1

DIVISION OF RESEARCH SERVICES

Summary of Program Activities
Calendar Year 1960

The Division of Research Services, which employs approximately 900 persons with almost 200 individual occupational skills, provides scientific, technical, and engineering services to support and further the research programs of the National Institutes of Health. The Division is composed of an Office of the Chief and eight branches: Computation and Data Processing, Instrument Engineering and Development, Laboratory Aids, Library, Medical Arts and Photography, Plant Engineering, Research Facilities Planning, and Sanitary Engineering.

DRS Programs -- 1960

Operated and maintained all NIH buildings, utilities, and grounds, and installed and helped maintain various types of equipment.

Provided design, engineering, and construction services for the comprehensive NIH building and remodeling program.

Coordinated the planning of all construction and remodeling work, and conducted engineering and architectural studies to assure the orderly development and growth of NIH facilities.

Initiated consultation services to universities, hospitals and other private organizations engaged in planning new medical facilities.

Provided photographic, art, library, and translating services to all of NIH.

Produced and supplied laboratory animals and media for use in NIH research.

Provided comparative pathology services for the control or eradication of diseases in laboratory animals.

Provided veterinary services, including diagnosis, surgery, X-ray, and animal quarantine, in support of NIH research projects.

Designed, and fabricated scientific apparatus, glassware, electronic equipment, and medical and surgical instruments not obtainable from commercial sources.

Designed, tested, and maintained mechanical apparatus for research, clinical, and office needs.

Designed, installed, maintained, and tested electrical, water, waste disposal, and other utility systems throughout NIH.

Washed, sterilized, and repaired NIH laboratory glassware.

Studied and improved all aspects of environmental health and sanitation at NIH, including food service facilities, air pollution, and insect and rodent control.

Provided various engineering and specialized services in support of germ-free animal investigations at NIH.

Provided centralized computation and data processing services and conducted research in the field of data processing directed toward widening the application of electronic computer and automatic processing techniques to NIH research programs.

Sponsored, conducted, and participated in job-related training courses covering a broad spectrum of employee occupational skills.

Accomplishments

Construction

The Division of Biologics Standards building was completed and occupied in July 1960. Construction continued on the Dental Research Building, the General Office Building, the Surgical Wing to the Clinical Center, and the National Library of Medicine. The first of two extensions to the Heating and Refrigeration Building, to provide air conditioning services to the new facilities, was completed, and work was begun on the second extension. Programs of requirements were developed for the proposed National Cancer Institute building, the Mental Health-Neurology building and for an extension of Mental Health research facilities in Lexington, Kentucky. Through its Research Facilities Planning Branch, the Division continued to maintain close liaison with construction activities at the National Library of Medicine because of NIH's future responsibility to provide operation and maintenance services for the building.

NIH Animal Farm

In May 1960 NIH purchased a 513 acre farm in Montgomery County, twenty-five miles from Bethesda. Operation of the farm, custodial care, and animal production will be the responsibility of the Division of Research Services. The farm is essentially an extension of the animal production and holding facilities on the NIH reservation. It will also enable the Institutes to undertake long-term studies with large animals in connection with chronic disease investigations and provide an isolated rural setting for the study of animals in their natural environment. Temporary alterations to existing structures were begun in 1960 and made possible the transfer of some animals from Casey Farm. Completion of the temporary alterations, which will allow NIH to vacate the Casey Farm, is expected in 1961.

A ten-million dollar program has been projected over the next four years for the construction of permanent large-scale facilities for animal research and production on the farm. A farm Master Site Plan to insure the orderly development of the construction program has been endorsed by the NIH Research Facilities Advisory Committee and approved by the Director, NIH.

Computer Program

The use of the IBM-650 computer in support of research programs and administrative operations reached a new high in July 1960 with the computer operating almost at full capacity. As a result of studies to determine future NIH needs for EDP equipment, a letter of intent was issued to the Minneapolis-Honeywell Corporation expressing NIH interest in renting a Honeywell-800 computer. A detailed report documenting the reasons for selection of the Honeywell-800 was prepared, and the selection was approved by PHS and DHEW. Installation of the new computer is planned for late 1961.

Controlled Maintenance

In 1959 a management consulting contract was awarded to the A. T. Kearney Company to develop and assist in the implementation of a controlled maintenance program for NIH. During 1960 considerable progress was made in preparation for the program, including establishment of a work control center, recruitment of key personnel, development of work procedures, trouble-call procedures and necessary forms, and precise determination of the scope of the program and inspection frequencies. As the year ended, installation of the program was in progress. It is scheduled for completion in early 1961.

Training

There was a substantial increase in the in-service and out-service training of Division employees during 1960. Approximately sixty employees attended job-related courses offered by universities and industry. Thirty supervisory employees attended a course in management techniques developed and presented by the Division. This course will be repeated in 1961. The course in animal care techniques, introduced in 1959, was continued. A nine-month course in refrigeration and air conditioning was begun by the Plant Engineering Branch in November. Detailed training plans submitted by all of the Division's branches indicate that formal employee training will continue to increase during the next two years.

Organizational Changes

There were several major organizational changes in the Division during 1960 designed to strengthen service areas and to increase their contribution to NIH research programs.

Three new branches were created:

1. Library Branch, effective April 20, 1960. Elevation of the NIH Library to branch status reflected a recognition of its continuing growth and of its contribution to the NIH scientific community. The reorganization has

made it possible for the Library to recruit additional professional staff members, to strengthen its various services, and to initiate plans for making the Library more responsive to the changing needs and problems of NIH scientists and investigators.

2. Computation and Data Processing Branch, effective May 8, 1960. Establishment of this branch involved the transfer of the biometrics functions of the former Biometrics Branch, DRS, to the National Heart Institute and extensive reorganization of the former Statistical Processing Section. Recruitment of an outstanding mathematician as branch chief and of competent mathematicians and programmers enabled this Branch to expand the application of its computer and data processing services to NIH research programs during the last half of 1960. It also made it possible for the Branch to undertake research in the general field of data processing, with a view to widening the scope of applications of mathematical, electronic computer, and automatic data processing techniques to biomedical research.

3. Instrument Engineering and Development Branch, effective May 8, 1960. This branch, the successor to the Instrument Section of the Laboratory Aids Branch, was established as a means of giving recognition to the instrumentation staff's professional status and vital relationship to medical research, and of providing leadership in advanced mathematics, physics, electronics engineering, and the application of technology to biology.

In December 1960 the name of the Scientific Reports Branch was changed to Medical Arts and Photography Branch. This change was made to reflect the narrowing in the functions of the Scientific Reports Branch resulting from the transfer of the Editorial Section and the Publications and Reports Section to the Office of Research Information and the elevation of the Library Section to branch status.

Problems

Recruitment

The Division of Research Services experiences difficulty in recruiting qualified mathematicians and engineers at the GS-9 and above level. The problem was of particular significance during the past year in the Division's instrumentation and data processing activities, which were advanced to branch status, and in the Plant Engineering Branch, where organizational changes and increased workloads, especially in design, resulted in the need for higher-grade engineers. There are two major elements to the problem. First, Government salaries for professional and technical positions in mathematics and engineering are generally not competitive with those in industry. Second, it is often difficult to find applicants who have the educational and experience qualifications for the specific jobs to be filled, with the result that the Division must recruit higher-grade individuals who, while they meet general job requirements as established by the Civil Service Commission, are not prepared to perform their duties without considerable training.

Budgeting Procedures

As indicated in last year's report, the budgeting procedures do not permit the degree of flexibility that would permit the Division to respond to increases and variations in the needs of NIH research programs. Placement of the Computation and Data Processing Branch under the Revolving Fund in 1960 has partially alleviated the problem in that area. However, the Glassware activity still presents a problem, particularly with respect to financing glassware replacement, and procedures for budgeting and scheduling major repair and improvement projects are still not entirely clarified.

ANNUAL REPORT ON RESEARCH PROJECTS

Division of Research Services

Calendar Year 1960

Although research is not the primary mission of the Division of Research Services, a limited amount of applied research is performed in the Division for the purpose of improving the quality of its services. The success of this effort is closely associated with the Division's ability to recruit and hold competent research-minded professional people who appreciate the quality of services required for research and who are willing to participate closely in the NIH research program.

During 1960, the research of the DRS was associated primarily with the programs in animal production, automatic data processing, environmental health, and biomedical instrumentation. Its basic trend was toward improving the quality of technical services provided by DRS and the professional ability of the personnel responsible for providing these services.

Significant accomplishments in these applied research programs included successful experimentation with the use of ethylene oxide gas to sterilize germ-free equipment; development of a thermal detector for recognition and localization of circulatory shunts in the human heart; progress in the formulation of a mathematical system for analyzing chemical reactions that occur in conjunction with the migration of reacting species; and the use of skin-grafting exchanges to determine the effects of inbreeding on the relative frequencies of histocompatible genes in the mouse.

TABLE OF DRS PROJECTS, 1960

Medical Arts & Photography Branch

Serial Number	Title
3.1	Plastic Molds for Forming Heart Valve Prosthesis for Heart Surgery
3.2	Simplified Plastic Wrist Splint for Physical Therapy Use

Laboratory Aids Branch

Serial Number	Title
4.1	Continued Study in Contrast Radiography
4.2	Surgical Lengthening of Long Bones in the Dog
4.3	Complete Surgical Hypohysectomy in Dogs
4.4	Improved Animal Husbandry Practices
4.5	Complete Removal of the Pineal Body of the Dog
4.6	An Abdominal Window for Viewing the Viscera of a Rabbit
4.7	Testing of Castiplast 11, 17 and 327 (Resins of the Epoxy Type) in Tissue
4.8	Study of Bovine Ocular Squamous Carcinoma
4.9	Rumen Fistula Plugs for Goats
4.10	Bacterial Resistance to Medication in Monkey Dysentery
4.11	The Effect of Repeated Shigella Challenge on Monkeys
4.12	Experimental Production of Vitreous Detachment in Dogs

Laboratory Aids Branch Cont'd.

Serial Number	Title
4.13	Incidence of Blessig-Iwanoff Cystoid Degeneration in Dogs and Cats
4.14	Therapeutic Applications of Partial Penetrating Keratoplasty in Dogs
4.15	A Comparison of Six Types of Diets for Mouse and Rat Production
4.16	Research in Animal Husbandry Practices and Procedures
4.17	Development of Histocompatibility Lines Derived from Two Inbred Strains of Mice
4.18	Effects of Inbreeding on Relative Frequencies of Histocompatible Genes in the Mouse
4.19	A Study of the Gross and Histopathological Characteristics of the Diseases of Rhesus Monkeys Before, During and Following Transport from India to U.S.A.
4.20	A Study of the Gross and Histopathological Characteristics of Diseases of Laboratory Animals Quarantined by the Animal Hospital Section
4.21	A Study of the Naturally Occurring Diseases of Laboratory Animals
4.22	Investigation of the Problem of Urinary Stones in Mice
4.23	Clinical Laboratory Examination of Animals Held in Quarantine in the Animal Hospital
4.24	A Study of the Spread of Tuberculosis from Infected Monkeys to their Cagemates
4.25	Investigation of the Viral Disease of Cats Held in Quarantine at the Animal Hospital, National Institutes of Health

Laboratory Aids Branch Cont'd.

Serial Number	Title
4.26	Filariasis in Quarantine Laboratory Animals
4.27	Fluorescein Amine Media for Rapid Differentiation of Staphylococci

Computation & Data Processing Branch

Serial Number	Title
5.1	Calculation of Transients in Muscular Contraction
5.2	The Kinetics of Chemical Reaction of Migratory Systems
5.3	Studies of the Mathematical Foundations of Theories of Color Vision
5.4	Nonlinear Least Squares Fitting

Sanitary Engineering Branch

Serial Number	Title
6.1	Evaluation of Gas Sterilization Equipment
6.2	Evaluation of Sanitizer-Detergent Compounds for Use in Patient Areas
6.3	Germ-Free Systems Research and Development
6.4	Germ-Free Guinea Pig Diet Development
6.5	Staphylococcus Studies (Air Contamination)
6.9	The Effects of Ventilation and Other Variables on the Bacteriological Quality of Air at the Surgical Wound Site

Table of DRS Projects, 1960

Instrument Engineering and Development Branch

Serial Number	Title
8.1	Thermal Detector for Recognition and Localization of Circulatory Shunts in the Human Heart
8.2	Direct Reading of Percentage of Oxygen in Blood Stream
8.3	Automatic Perfusion Apparatus for Removal and Collection of Radioactive Effluents
8.4	Electronic Method of Converting Percent Transmission to Optical Density
8.5	Instrument for Maintaining Precise pH Control of an Enzymatic Reaction (pH Stat.)
8.6	Precision-Timed Light Interrupter for Ultraviolet Illumination of Microscopic Specimens
8.7	Radio Frequency Energy Effects on Biological Materials

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities 1. DRS-2 Serial Number

2. PLANT ENGINEERING BRANCH 3. R. R. Holliday Branch Chief

Objectives and Programs

The objectives of the Plant Engineering Branch are to provide three major central services. These are:

Operation and Maintenance: These services consist of operating, maintaining and repairing NIH physical, mechanical, electrical, architectural and landscaping facilities, as well as maintaining and repairing laboratory and research apparatus.

Engineering Services: These services consist of developing and preparing plans and specifications for alterations, repairs and extensions to the existing facilities, administering and inspecting construction work performed by private contractors, and providing professional engineering services for planning new buildings and facilities.

Construction Services: These services consist of altering, installing and fabricating facilities and equipment for research programs. In this capacity the Branch furnishes mechanical, electrical and architectural craft services.

The above services are provided by the five sections of the Branch and the Office of the Chief. The five sections are: Planning and Control, Engineering Design, Maintenance Engineering, Shops, and Grounds Maintenance and Landscaping.

PLANNING AND CONTROL SECTION: Responsible for the planning and control of all PEB work including receipt, review, classification, planning craft work which does not require professional engineering skills, estimating, scheduling and routing; for the continuous inspection of NIH facilities; for the review, recommendation and justification required in the funding of maintenance and repair, and alteration and construction; for the administration and inspection of all work performed by outside contracting firms; and for the administration, operation and control of the Branch Shop Stores.

ENGINEERING DESIGN SECTION: Responsible for matters pertaining to engineering studies and reports; engineering design, including development of plans and specifications; and the maintenance of the Plant Engineering Branch technical plan files and records.

DRS, Plant Engineering Branch, cont'd:

MAINTENANCE ENGINEERING SECTION: Responsible for administration and for the operation, operational maintenance, trouble shooting and operator inspection of the heating plants, refrigeration plants, incinerator plant, substation, building mechanical-electrical equipment and systems, including air conditioning, pumping, communications, elevators, can wash equipment, laundry, etc. Also electric, water, steam, sanitary, air, gas, chilled water, distilled water and fuel oil distribution systems.

SHOPS SECTION: Responsible for administration and operation of the craft shops engaged in performing maintenance and repair, and alteration and construction for all of the NIH except that performed by private contractors.

GROUNDS MAINTENANCE AND LANDSCAPING SECTION: Designs new landscaping for the NIH Reservation and provides professional consultation. Maintains, develops and renovates the grounds of the Reservation including woodland, lawns, shrubbery, trees, flowers, and ground cover material, station roads, service areas, parking lots and walks (including snow removal and ice control). Responsible for maintaining and operating equipment required for such work as excavation, concrete removal and light and heavy rigging. Maintains indoor plantings in various buildings of the Reservation and supplies other ornamentations appropriate to the various occasions and/or seasons.

Accomplishments

REGULAR WORKLOAD

Alteration and Construction: The shops completed 4125 alteration and construction jobs for the NIH Institutes and Divisions during the first eleven months of the year. This work required 91,377 man-hours which cost approximately $319,820. The material costs for this work were $123,401. This does not include work performed under our new trouble-service procedures. Data concerning this subject are included under the Controlled Maintenance Program.

Maintenance: The Branch operated, maintained and repaired the following facilities:

1. Medical research and service buildings having gross floor space of 2,770,571 square feet. The supporting utilities including major utility plants for heating, air conditioning and incineration.
2. 307 acres of landscaped grounds.
3. 7 miles of paved roads.
4. 28,000 linear feet of sidewalks.
5. 30 acres of parking lots.
6. Poolesville Farm - 498 acres.

During the first eleven months of the year, the Branch completed 6882 specific projects identifiable to maintenance and repair. This work required 305,748 man-hours which cost approximately $1,070,118. The material cost for this work was $129,764. This does not include the maintenance work performed under our new trouble-service procedures.

The Branch took over operation, maintenance and alteration of the new building for the Division of Biologics Standards (Building 29). The shops have expended approximately 5,000 man-hours of effort in connection with alterations required to move personnel from the old buildings to the new.

Contract Administration: The Branch administered and inspected 118 NIH construction contracts during the year. Cost: $1,989,175. In addition, the Branch inspected and assisted the Regional Office, Public Buildings Service, with the administration of 16 repair and improvement projects contracted for NIH. Cost: $921,045.

Engineering Design: In addition to engineering devoted to work performed by the Plant Engineering Branch Shops, new building construction and special engineering studies, plans and specifications were prepared during the past year for 43 construction and alteration projects performed by outside contractors. The total construction cost of these projects is estimated at $1,515,000. In all, some 325 work requests requiring design by professional engineers, representing nearly two million dollars in construction costs were processed during the past year.

Major Projects: The following major construction and alteration projects were designed during the year and are in varying stages of construction. The total estimated construction cost is indicated in parenthesis for the cited work in each building or group of buildings.

Building 5 ($300,000): A general rehabilitation of this building is scheduled after the transfer of personnel into the new Building No. 29. This work includes the renovation of 78 laboratory modules and 7 animal rooms, alterations to the existing Insectary, and the installation of new and supplementary air conditioning, hood exhaust, electrical distribution and lighting systems throughout the building.

Building 8 ($325,000): The Germfree facilities in this building are being renovated and extended to occupy the entire third floor. The second floor is being converted from offices to laboratory space, involving replacement of plumbing and electrical distribution systems and the installation of new air conditioning and general exhaust systems. The latter mechanical systems have been installed to accommodate conversion of the first floor to laboratory space during 1961.

DRS, Plant Engineering Branch, cont'd:

Building 10 ($240,000): A low level radiation counting facility is being constructed in the sub-sub basement for the purpose of housing instrumentation to count radio-activity in the human body and other objects. Two room-size cubicles are being erected, with 6" thick steel walls, floors and ceilings, to provide isolation from outside radiation influence.

The Wm. A. White Building, St. Elizabeths ($92,000): A portion of the ground floor of this building was renovated to provide laboratories and an instrument development shop area for neuropharmacology research work.

Other Research Buildings ($183,000): Air conditioning and ventilation problems will be corrected in Building 3 by proposed modifications to the existing central air conditioning system and the addition of new air conditioning and ventilation equipment to serve the animal areas on the attic floor. Cooling coils were added to the existing S-2 makeup air unit in Building 4, thereby permitting installation of laboratories on the sub-basement level and relieving the shortage of conditioned air throughout the building. At the same time, conversion of an existing DC electrical distribution system to AC service permitted the renovation and installation of several new laboratory facilities in Building 7. Half of the west basement area in Building 9 was converted to research use by the construction of five specially constructed, relatively soundproof cubicles for animal studies. Two specially designed chambers, requiring high intensity lighting and carefully controlled humidity and temperature conditions, were constructed in Building 32 to carry out plant growth experiments in enzyme and alkaloid yield.

Renovations to Service Buildings and Other Areas ($280,000): Modernization of the cafeteria kitchen in Building 1 was accomplished, and air conditioning equipment is being added to the ventilation system serving the main kitchen in Building 10. The Statistical Processing area on the ground floor of Building 12 was expanded and renovated, including conversion of existing air conditioning equipment and the addition of new air conditioning units and exhaust fans to serve the increased requirements. The north portion of the second floor of Building 13 was renovated to provide 11,000 square feet of office space for Plant Engineering Branch, Research Facilities Planning Branch and Director's Reserve. A pneumatic tube system has been designed to serve both of these areas in Buildings 12 and 13. Renovation and rehabilitation of existing walk-in cold boxes in Building 13 is being accomplished to provide dependable storage facilities for frozen blood serum collected in a nationwide cerebral palsy study intended to run for a minimum period of ten years. Renovations of space in Buildings 14-A and 28-A were accomplished to facilitate relocation of the Laboratory Aids Branch from Building 10.

DRS, Plant Engineering Branch, cont'd:

NIH Farm Improvement and Temporary Construction $130,000): Improvements are being made to the tenant house and other existing farm buildings at the NIH farm, Poolesville, Maryland. The design for the construction of an Animal Quarantine Building, which consists of 6,700 square feet of enclosed space and 2,650 square feet of exterior runs, has been completed.

STUDIES AND SURVEYS

The following studies and surveys were made during the past year:

Utility Site Plans: Hundredth scale, reproducible ink drawings were prepared to show all of the services and underground distribution systems (except storm sewer) on the NIH reservation. Development of these drawings was based on information taken from recent surveys made by other NIH organizations and outside consultants, and the knowledge of the existing utilities obtained from Plant Engineering Branch operating and shop personnel. It will be the continuing responsibility of the Engineering Design Section, Plant Engineering Branch, to keep these site plans up to date to reflect the "as-built" condition of NIH utilities and services.

Chilled Water System: A study of the central chilled water system is being conducted to determine how this system should be developed and utilized for efficient and economical operation to serve present and future chilled and cooling water requirements. The first recommendation to come out of this study was that all air conditioning requirements in the comfort range should be served from the central refrigeration plant by connection to the existing chilled water distribution system, if at all possible. Some of the apparent advantages for utilization of a central system over the installation of separate direct expansion refrigeration equipment are as follows:

1. Less mechanical space required in the occupied building.

2. Reduction in electrical power requirements in the occupied building.

3. Elimination of noise and vibration from refrigeration compressor, cooling towers, etc. in the occupied building.

4. Reduction of total maintenance and operating requirements.

5. Reduction in total electrical power requirements because of increased efficiency in central refrigeration plant operation. In the NIH plant, electrical power requirements will be further reduced by the utilization of steam in operating proposed new refrigeration equipment.

In line with the above recommendation, the chilled water distribution system was extended into Buildings 3, 8 and 12 this past year. Existing air conditioning systems were converted or new air conditioning systems were installed in Buildings 3, 4, 5, 8, 9, 10, 12, 13 and 28, at an estimated

DRS, Plant Engineering Branch, cont'd:

installation cost of $375,000, thereby adding a total load of approximately 880 tons to the central refrigeration plant in Building 11.

Sewer Usage Savings: A net savings of $2,412.48 was realized through the use of separate water meters on the air conditioning towers of the central air conditioning system. Last spring it was observed that water used in the air conditioning system was not being returned through the sanitary sewer system, and should therefore not be subject to sewer usage charge. Separate metering of the cooling towers resulted in deduction of the 16¢ per 1000 gallons sewage charge for the water used in the air conditioning system, with net savings as above for the total season.

GROUNDS AND LANDSCAPING

General: Since weather is probably the most important single natural factor that affects Grounds operations, a quick review of the 1960 weather conditions is in order.

January and February, both relatively mild, brought moderate moisture, all in the form of rain. Three heavy snows in March, each one week apart, helped replenish deep soil moisture. However, April proved to be one of the driest on record. Just one month after the last spring snowfall, this area experienced a record hot spell of three days that reached 95°.

The rest of the year was relatively cool, with frequent light rains that kept lawns green all summer and shrubs and trees growing steadily. Several heavy flash rains tested the new creek project but did not leave much moisture behind in the soil.

Autumn and early winter were mild and relatively dry. As a result, the leaves were very slow to fall, a fact which caused much extra work in this area.

Generally, the 1960 weather was conducive to good growth of lawns, shrubs and small trees. It was also conducive to insect development and spread of diseases such as fire blight, rusts, mildews and black spot.

Owing largely to the new building construction, the overall appearance of the reservation has suffered from the unsightly piles of earth, construction debris and materials, and torn up, dirty streets.

Lawns: The soil conditioning and fertilizing program was continued and appears to be helping. NIH lawns did not experience as much burning during hot dry periods and the terrific spring growth peak that caused so much trouble in past years did not occur. Slow acting fertilizers and the use of organic conditioners are accomplishing this.

Trees and Shrubs: For the past several years trees and shrubs from new construction sites have been salvaged. Most of these were transplanted to other locations immediately, such as along the convent fence. Others that were not in good healthy condition were placed in the nursery at

DRS, Plant Engineering Branch, cont'd:

Stone House to develop. This fall, a new hemlock screen between Buildings 1 and 8 and foundation planting across the entire east side of Building 1 were planted with these reconditioned salvaged plants.

Insects and plant diseases have kept spray crews busy applying seven complete coverings to the entire reservation, using approximately 70,000 gallons of diluted spray material; Malathion, DDT, Captan, Phaltan, Methoxychlor and Dormant oil. Some plants, such as fruit trees, required twelve sprayings.

Streets, Walks and Parking: Street and parking repair has been confined mainly to patching broken areas and sealing joints in concrete paving. Wilson Drive and Stone House Road were resurfaced with temporary treatment of tar and chips in an attempt to get these two badly deteriorated streets through the coming winter without mudholes.

The concrete circle drives in front of Building 10 and Building 1 were resurfaced with 1-1/2" of asphalt to stop the spalling of the concrete and improve the appearance of these two prominent areas.

Heavy construction traffic will necessitate extensive and costly road repair and renovation in the near future. The snow control program got an excellent trial in March. Several areas needing improvement were found, mainly the training of crews. This training is particularly difficult because actual conditions are best for it, but then the need for speed in clean-up often forces one to neglect the individual worker and hope for the best.

The increased use of chemicals probably helped most by keeping the surfaces from freezing, facilitating plowing and shoveling. This year "Banox", a chemical additive to rock salt that inhibits corrosion, was used.

Master Landscape Plan: The Grounds Maintenance & Landscaping Section is moving rapidly ahead on a master landscape plan. Planting plans are now being prepared for Buildings 1 through 9 and are 75% complete. Quarters 15-I, Building 1 and Buildings T-18 and T-19 have been planted as the initial steps in actually implementing this plan.

NIH Farm: The new animal farm at Poolesville, Maryland, has been the scene of heavy, though sporadic activity for the Grounds Maintenance & Landscaping Section. Most of the old, deteriorated fencing has been removed; new fencing (4,000 feet) has been installed; and some overgrown fence rows have been cleaned out. The pastures (250 acres) have been limed, fertilized, and overseeded; all pastures were mowed at least six times. The old farmhouse and storage barn will be demolished as soon as certain electrical changes are made.

Changes and Improvements

REORGANIZATION OF THE BRANCH

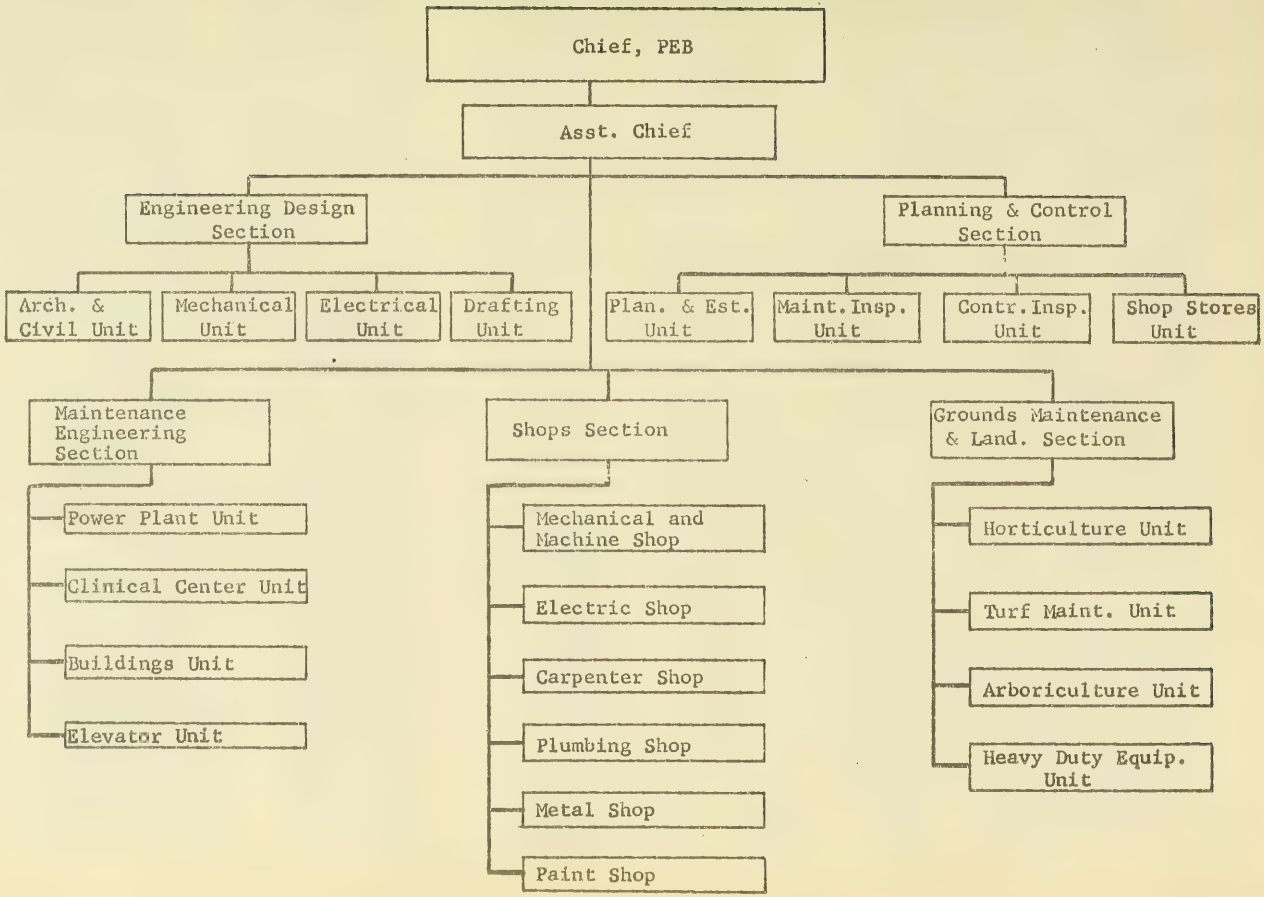
A complete reorganization of the Plant Engineering Branch down to the Unit level was completed in October of 1959, details of which were described in last year's report. During 1960 the principle effort in this area was devoted to bringing the staff up to complement. The current organization chart of the Branch is shown on the next page.

Late in 1959, following an analysis of workload trends, it was decided that the then existing craft sub-shops in the Clinical Center which reported to their respective main shops in Building 13, would be eliminated. This has been done. The Maintenance Engineering Section which has had primary responsibility for day-to-day operation of the NIH plant, during the past year has been assigned a limited number of additional personnel from the skilled trades, which has permitted them to receive trouble-service calls directly and handle them expeditiously, using short-cut planning and dispatching methods. Under previous procedures, with all requested work being handled by the craft shops, the very large volume of work had made it necessary to defer many smaller jobs because of the pressure generated for assignment of personnel to major alteration work. In addition, procedures required for handling larger multi-craft alteration jobs did not lend efficiency to the handling of trouble-service work involving only one craft for several hours.

During the past year the transfer of trouble-service call responsibility to the Maintenance Engineering Section has been completely implemented, including the development of internal dispatching procedures. The improvement in service being rendered in this area has exceeded expectations. It is now possible to furnish service on a large percentage of trouble-service calls in two hours or less and, since nearly 50,000 such calls are handled per year, this constitutes major progress.

When the present NIH building construction program was begun several years ago, it was anticipated that an additional organizational unit of operating engineers would be required to handle the new buildings. Under the Branch reorganization, completed in 1959, provision was made for a North Buildings Operating Unit and a South Buildings Operating Unit, the latter unit to be activated upon completion of Building 31. However, as the requirements were re-reviewed during implementation of the Controlled Maintenance Program, it became evident that more effective control and service could be obtained through consolidation of functions within the existing operating units rather than by creating additional units, and the operating units were accordingly reorganized along these lines. Therefore, plans for the South Buildings Operating Unit have been cancelled and all building responsibilities have been assigned to the Clinical Center Unit (Building 10 only), the Power Plant Unit (Building 11 only), the Buildings Unit (all other buildings), and the Elevator Unit, which is responsible for all elevators on the reservation.

August 25, 1960



DRS, Plant Engineering Branch, cont'd:

In addition to the changes outlined above, procedures were developed during the year under which all labor of the operating units of the Maintenance Engineering Section will be dispatched, using the same techniques as are applicable for other Plant Engineering Branch productive work under the Controlled Maintenance Program. For some time, as the number and complexity of NIH facilities have increased, it had been a matter of concern that there was an insufficient safety factor in relying on individual operating engineers to perform maintenance work without orderly direction. The solution has been to survey all of the items of equipment on the reservation, determine which items should be routinely inspected by operating engineers, and prepare operator shift routes which can be manned by available personnel. This will assure that those things that need attention are getting the attention required and that deficiency reports are submitted wherever equipment failures are found, permitting corrective action at an early date. The personnel in the operating units who formerly served as "senior building engineers" will be grouped in maintenance crews in each of the units to perform planned preventive maintenance, scheduled lubrications, etc.

Concurrent with the internal reorganization of the Buildings Unit, Maintenance Engineering Section, new headquarters for the Unit were established on the second floor, Building 13. This is the first time that this unit has occupied suitable and permanent quarters. There has been a noticeable increase in morale and productivity of personnel in this Unit since the reorganization and occupancy of the new quarters.

Preliminary planning for a similar reorganization of the Clinical Center Unit has been completed. The personnel are operating under the new procedures which were developed and plans have been made for rearranging the units, office and shop areas in order to permit more effective operation under the revised organization. Approximately 1200 square feet of space on the B-1 level of Building 10 will be released as a result of this rearrangement.

Planning for a minor reorganization in the Engineering Design Section has been completed and will be implemented early in 1961. In the past, there has been an expansion of professional and non-professional engineering and drafting personnel in separate groups. Under the new organization, the draftsmen will be interspersed among professional engineering personnel along the lines of professional doctrines, which will permit closer supervision and provide greater growth opportunities for the engineers-in-training and the sub-professional people.

Some reorganization of the Grounds Maintenance and Landscaping Section was accomplished during the year. The addition of the NIH Farm and expansion of NIH has dictated these changes. A new position of General Foreman was established and filled. This foreman has been given the responsibility for implementation of the day-to-day work of the Section, thus permitting the Chief of the Section to devote time to planning the work and preparing new landscaping plans. An assistant landscape architect was employed in a staff capacity to assist with planning the NIH reservation and farm programs.

Plans are now being made to establish two additional units in the section; one with responsibility for implementing programs for the new NIH farm, and the other for maintenance of streets, walks and parking areas.

DEVELOPMENT OF A SHOP STORES MANAGEMENT SYSTEM

A report entitled "Study of Maintenance Shops and Stores", completed December 6, 1957, by the management consulting firm of A. T. Kearney and Company, recommended that the then separate PEB shop stores be physically consolidated and placed under modern procedures of inventory and storeroom control. The study indicated that the Branch had in stock an average of 17.4 months supply of shop stores material, representing an investment of $439,800 and occupying 16,300 square feet of space. It was estimated that inventories could be reduced to an average six months supply, representing a $242,000 reduction in stock investment. Floor space could be reduced in proportion.

In January 1958, management of the PEB shop stores, which previously had been under administrative control of the respective shops to which they were attached, was consolidated into a single organization. In June of 1958, A. T. Kearney and Company was retained on contract to assist in the development and installation of new stock control and management procedures.

A more detailed analysis of stock material was made, which indicated that existing stock consisted of 12,590 separate line items, having a total inventory value of $435,550. New guide lines and control factors were developed to permit initial reduction in the number of line items to 6,550, having an average inventory of $116,600, or a total inventory reduction of approximately $318,950, and a saving of approximately $32,000 per year in carrying costs. (The above figures exclude construction materials financed through the NIH revolving fund).

As of the end of 1959, implementation of the new Shop Stores System was approximately 90% completed. During the year, shop stores stock was first merged into two temporary storeroom areas during renovation of the former Sheet Metal Shop area, after which the material was moved to its final location in a single, consolidated storeroom. Preparation of storage space for Revolving Fund material was completed. This material (laboratory cabinets, fume hoods, sinks, etc.) presently is required to be physically separated from all other stock.

Development of detailed operating procedures was completed, including completion of the "Shop Stores System Manual of Procedures" prepared by A. T. Kearney and Company, as part of their contract. Bundling and bagging of stock in appropriate control quantities, design, approval and procurement of special forms, supplies and office equipment was accomplished, and operation under the new control procedures was begun May 18, 1959. Experience gained from the first few months of operations permitted completion of management control procedures, which will be added as the final chapter of the manual of procedures.

DRS, Plant Engineering Branch, cont'd:

The following additional improvements in the Shop Stores System were made during 1960:

1. All items presently financed under the NIH Revolving Fund (laboratory cabinets, fume hoods, sinks, etc.) have been brought under the new stock control procedures. In addition, these items are now procured individually on a line-item basis rather than by large orders of miscellaneous equipment as was done in the past. It has been found that for many items of equipment, this procurement method has reduced lead time from as much as 5 or 6 months to approximately 30 days.

2. Format and method of reproduction of an adequate Plant Engineering Branch Shop Stores Catalog has been determined, requirements for necessary equipment have been prepared, and the equipment has been ordered. The Shop Stores Catalog in the future will be prepared and maintained by the Flex-O-Print process, which has previously been used at NIH for several years for the Central Storeroom Supply Catalog, issued by the Supply Management Branch, OAM.

3. A new storeroom requisition was designed and placed in use which was made possible by the shift in statistical processing work to the model 650 computer. This requisition form replaced four documents previously used, greatly reduced clerical time and resulted in a substantial reduction in errors inherent in the system previously used.

4. Staffing of the Shop Stores Unit was completed, including the hiring of a Supply Cataloger to prepare accurate and appropriate stock item descriptions.

5. A special material procurement unit was established to centralize in one location within the Branch, all requisitioning and follow-up procedures for special material required for construction, alteration and maintenance work performed by Plant Engineering Branch.

6. It was proposed last year that the Plant Engineering Branch Shop Stores system be placed under NIH Revolving Fund financing to be effective July 1, 1960. During the past year, personnel of PEB worked with representatives of Financial Management Branch in completing preliminary planning for this move. However, a decision was made at a higher level to defer placing the system under Revolving Fund financing until a later date.

7. Storage space for bulky construction materials and special material requiring long term storage, as well as specialized tools and equipment used seasonally by various organizations of PEB, was obtained in the basement of Building 14 and means provided for securing the material stored therein.

DEVELOPMENT OF A CONTROLLED MAINTENANCE PROGRAM

As part of the general reorganization of the Plant Engineering Branch, the nucleous of a central control point was established during 1958 for planning, estimating and scheduling the work of the Branch. During the first year of operation, all construction and alteration work (maintenance work was excluded) was processed through the central point, called the Project Control Office, as a result of which a substantial reduction was made in the average time between receipt and completion of projects.

Experience gained through operation of the Project Control Office led to the early conclusion that all work of the Branch, including maintenance, should be placed under modern management procedures. A decision was reached to obtain the services of an outside consultant to assist in establishing detailed procedures, and a contract was awarded for this purpose to A. T. Kearney and Company, Chicago, Illinois, on June 29, 1959. The program is referred to as the Controlled Maintenance Program, the term usually used in private industry and some government agencies where these management techniques have been adopted.

Planning of the Controlled Maintenance Program was begun immediately after award of the contract to A. T. Kearney and Company. The general scope of the program is as follows:

1. Initial Survey: Conduct a survey of the present mission, requirements and detailed procedures of the Plant Engineering Branch for planning and accomplishing maintenance and other assigned work.

2. Recommendations: Develop recommendations for the policies, staffing and duties required for a system of controlled maintenance of facilities, based on the following elements:

   a. Systematic and continuous inspection of all parts of the facilities.

   b. Detailed planning and estimating of all major work.

   c. Advance scheduling.

   d. Coordination of the availability of materials, equipment, manpower, tools, etc.

   e. Ready access to management of all pertinent data on manpower, costs, material and backlog of work.

3. Work Control Center: Within the framework of the approved policies and planned staffing, establish a work control center in the Plant Engineering Branch, including the following specific tasks:

DRS, Plant Engineering Branch, cont'd:

a. Develop the policies and procedures as required to receive, review, classify, authorize, route and record all work, including defining and establishing categories and types of work orders.

b. Develop and install an appropriate work order numbering system and simple internal cost accounting system in terms of labor and material.

c. Develop and install a system for accurately determining and recording the man-hours devoted to specific jobs, standing work orders, projects and other categories of work.

d. Collect and record the data required to establish work standards by statistical analysis; analyze the data and establish the standards.

e. Develop and install procedures for applying the work standards for labor loading, control, and backlog reporting, including the development and application of additional techniques such as estimating to supplement the work standards.

f. Develop and install the procedures for weekly scheduling of major jobs by shop crafts, including the application of operating procedures and data generated in the system to provide general indicators of work performance by craft.

g. Develop management reports as required and establish procedures for their preparation and use.

h. Establish the guides and methods for auditing the system to insure its continued effectiveness.

4. Preventive Maintenance: Within the framework of the approved policies, objectives and planned staffing, develop preventive maintenance procedures, including the following specific tasks:

a. Develop the policies and procedures for determining what facilities and items of equipment are to be inspected, and direct the preparation of detailed listings of items by categories, such as buildings and components, electrical, mechanical, etc.

b. Develop the procedures for determining what is to be inspected, frequency of inspection, etc.; apply the findings to the detailed facility listings and record the data in usable form as a master inspection guide.

DRS, Plant Engineering Branch, cont'd:

c. Develop and install the procedures for preparing an inspection schedule from the master inspection guide to provide the means for initiating the actual inspections and accomplishing routine maintenance work.

d. Integrate the preventive maintenance procedures into the over-all Controlled Maintenance Program, including development of procedures to spell out who will inspect, inspection routes, inspection methods, auditing and control reports.

Implementation of this program completed during 1960 was as follows:

1. An Interim Procedures Manual was completed, duplicated and distributed to key personnel.

2. The Planning and Estimating Unit of the Planning and Control Section was staffed and all work received by the Branch (other than trouble-service calls) is now received through this unit and is estimated as to labor and materials before release of the Shop Orders to the Shops Section.

3. With minor exceptions all productive labor of the Plant Engineering Branch is being dispatched to individual jobs under procedures in which accurate time records are kept for each job.

4. The Maintenance Inspection Unit of the Planning and Control Section has been staffed, rough drafts of inspection guides completed, agreement reached on facility items of NIH which will be included in the program and for which cost records will be maintained; all necessary supplies of forms have been obtained and a good start has been made in preparing basic facility records.

Progress made during 1960 on the Controlled Maintenance Program was not as great as had been anticipated, due to numerous delays in recruiting personnel for planning and estimating, shop planning and maintenance inspector positions. However, now that the staffing has been completed, the target date for completing implementation of the program is June 30, 1961.

Specific items for further implementation during 1961 are as follows:

1. Begin loading procedures.

2. Begin scheduling procedures.

3. Begin performance and cost reporting.

4. Devise procedures necessary for management aspects of the system.

5. Prepare and distribute the final operating manual.

DRS, Plant Engineering Branch, cont'd:

6. Begin generating preventive maintenance inspections and overhauls, from the Maintenance Inspection Unit.

7. Extend operations of the Controlled Maintenance procedures to the Grounds Maintenance and Landscaping Section.

8. Continue training of personnel in order to obtain maximum benefit from the new procedures.

Improvements in Contract and Procurement Procedures: During the past year, delays in procurement of stock and special material processes through formal procurement channels have become increasingly critical and have resulted in many delays in the completion of construction, alteration and maintenance work. The Procurement Section, Supply Management Branch, was aware of the problem and made many efforts to expedite particularly urgent items. Finally, a meeting with Branch representatives to search for some permanent solution to the problems was held. A number of proposals were made covering both procurement of supplies and material expended by NIH station labor as well as contracting procedures for work performed by contract. The following procedures were adopted:

1. Informal contract procedures: Previously, the Plant Engineering Branch has been authorized to solicit bids for informal contracts for work not exceeding $500. The limitation on these procedures has been increased to $2,000 which is the maximum dollar ceiling authorized for NIH. Under this arrangement, when it is determined that urgent work falling within the dollar limitation cannot be accomplished by station labor, it will be possible to very quickly obtain informal contracts and give expeditious service. This type service was not possible in the past because of the paper work involved in preparing detailed plans and specifications and the time required for solicitation, review and award of contracts.

Additionally, a program has been initiated to develop standard specifications wherever possible for types of construction which occur repeatedly. One engineer has been assigned full time to developing informal contract specifications and standard specifications, and another engineer is being recruited to assist with this work.

2. Improvements in Procurement Procedures: The Procurement Section, Supply Management Branch, OAM, has delegated authority to PEB to place telephone orders with approximately 45 local suppliers for stock and special material, the only limitation being that each order must not exceed $50. Also, the Branch has been authorized to prepare cash pick up tickets and to prepare direct purchase orders for material which must be obtained from suppliers outside the Washington area. These procedures cover approximately 90% of all the Branch's material requirements and have made possible tremendous improvements in obtaining material. Prior to the initiation of these procedures it had taken as long as two months before purchase orders were written, plus the time required for delivery of material, whereas

today, a great proportion of our material requirements can be satisfied and delivered from the vendor within 24-48 hours after the order is placed.

Operation of PEB Motor Pool: Effective November 21, 1960, PEB initiated pool operation of all motor vehicles assigned to the Branch (except those assigned to Grounds Maintenance). Sixteen vehicles are involved, which are now under an orderly dispatching arrangement under the administrative control of the Chief, Shops Section. The purpose of the pool operation is to (1) obtain better vehicle utilization, (2) insure availability of vehicles when required, (3) insure adequate and proper vehicle maintenance and (4) comply with mandatory vehicle operating and record-keeping requirements.

TRAINING

Personnel of the Branch received a total of 292 man days of training during the year. Of this, approximately 177 man days were in technical subjects directly related to the job. The remaining 115 man days were devoted to administrative or supervisory training, ancillary to the official job. Course titles are a key to the range of the training taken advantage of by Branch employees: Instrument Maintenance and Repairs, Temperature Controls, Engineering Administration, Negotiated Contracting, Reading Improvement, Electrical Engineering Review, College Algebra, Accounting, Secretarial Clerical Training, Personnel Administration, Commercial-Industrial Oil Burning and Equipment, Supervisory Training, Occupational Safety, Heating & Power Conference, Steam Boiler Management, Plain Letter Writing Course, Review of Basic Engineering Subjects and Related Sciences, Operation of Vibration Analyzing Equipment, Pneumatic Controls as Related to Building 29 Controls, Pneumatic Controls as Related to HV and AC, Centrifugal Operations, Polyfusion of Vulcathane Pipe, Principles in Techniques and Skills in Office Administration.

This year, for the first time, training in supervisory techniques was offered at the line supervisory level. Eight line supervisors took advantage of this course, sponsored by the Division of Research Services, involving approximately 40 man days.

PERSONNEL RECRUITMENT

Branch personnel increased from 394 as of December 31, 1959, to 436 as of December 13, 1960, a net increase of 42 employees. Most of the increase in personnel occurred in the Engineering Design Section, which expanded from 17 to 25 employees, and in the Planning and Control Section, which grew from 22 to 38 employees during this period. These increases are especially significant for the overall Branch program, since they represent on the one hand, addition of much needed professional engineering skills, and on the other, addition of planner-estimators and maintenance inspectors, essential to the implementation of the Controlled Maintenance Program. By the same token, many of the additions to the Planning and Control Section came from promotion of the craftsmen of the Maintenance Engineering Section and the Shops Section, so that the increase in one area resulted in a reduction in craft personnel in the other.

DRS, Plant Engineering Branch, cont'd:

Recruitment is underway, however, for all remaining craft vacancies and it is expected that the majority of these will be filled by early 1961. Reductions in force in some of the nearby defense agencies are making it considerably easier to hire this kind of worker at the present time.

December 1960 Calendar Year 1960

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-3
Serial Number

2. MEDICAL ARTS AND PHOTOGRAPHY BRANCH

3. James A. King
Acting Branch Chief

Objective

To improve the quality and increase the applications of medical arts and photographic services to NIH research programs by keeping abreast of new developments and trends in the medical art and photography fields, increasing the competence of the Branch's technical staff, and cultivating a closer working relationship with the scientific staff of NIH.

Programs

The Branch provides a variety of highly specialized medical art and photographic services in support of the programs of the Institutes and Divisions of NIH. Medical art services include scientific exhibits, medical and general illustrations, graphic arts, statistical drafting, varityping, moulages, and plastic models. Photographic services include medical photography, photomicrography and gross pathology, motion pictures, slides and slide sequences, and news photography. Consultation is provided to NIH scientific and administrative personnel on the application of medical arts and photography to their programs.

Progress and Accomplishments

MEDICAL ARTS SECTION

During 1960 the Section completed approximately 6 per cent more service requests than in 1959 and successfully handled an increasing number of complex projects calling for the development and application of novel ideas and techniques. These accomplishments were made possible in part by the addition of six new staff members.

Following is a list of the Section's more significant accomplishments during the year

Exhibits. Nineteen new exhibits were produced, five of which won awards. In addition, five existing exhibits were substantially modified. Two important changes related to the design and construction of NIH exhibits were introduced and are helping to reduce some of the more serious problems of exhibit production: first, crate dimensions have been standardized to facilitate shipping and storage; second, the Medical Arts Section now reviews

all exhibit construction plans before contracts are awarded, thereby reducing the chance of mistakes in design or cost of exhibits produced under contract. To further reduce problems, work was begun on an exhibits guide designed to provide information to NIH personnel on materials, procedures, etc., relating to NIH exhibits.

New Style for Lecture Slides. A simplified style for lecture slides was introduced to improve the effect of the slides and reduce production time. Colored paper cut-outs are mounted slightly above the surface of the background. The cut-outs cast shadows on the background during the photography process, thereby making possible a striking three-dimensional effect without laborious hand painting.

Standardization of Art-work for Slides. The size of original art-work prepared for slides has been standardized to simplify photography and production.

Psychological Testing Illustrations. At the request of NIMH, a series of psychological testing illustrations were created, consisting of 17 steps, beginning with a male head, transforming into a neuter personality, and culminating in a female head. The series forms part of a study of the decision-making ability of various groups of individuals and is being used in conjunction with another series of abstract shapes and of changing animal configurations.

Silk-screen Equipment Installed. The silk-screen process expedites the application of lettering to exhibits, makes it unnecessary to contract for this work, and reduces the requests to the Photography Section for hot-press lettering on overlays for art work in slide series. It is extremely versatile and is useful over a broad range of art-work.

Schematic Illustrations of Intraocular Venous System. A series of schematic composite illustrations were prepared for NINDB, demonstrating the radiographic anatomy of the intraocular venous circulation of the cat. Through the application of an intricate radiographical technique to intact living eyes, NINDB investigators were able for the first time to describe the complex intraocular venous circulation of the eye of a cat.

Illustration Studies of the Monkey. Drawings from careful observations of the attitudes and behavior of the monkey were prepared for NIMH for use in studies of the basic motivating forces in man. The drawings will be used for lecture purposes and for publication in medical journals.

Illustrations of Significant Eye Diseases of Animals. A high rate of eye diseases has been found among animals passing through the DRS Animal Hospital. Illustrations of the color and structure of diseased eyes have been prepared by direct and indirect opthalmoscopy. Their publication should do much to awaken veterinarians to the necessity of careful animal eye examinations.

Illustrations of Experimental Heart Studies. In support of NHI research directed toward the ultimate goal of transplanting living hearts, illustrations were prepared from direct observation of heart operations on dogs.

DRS, Medical Arts and Photography Branch, cont'd:

Illustrations of the Angle of the Eye. A gonioscopic lens was used to prepare illustrations of the angle of the eyes of NINDB glaucoma patients.

Illustrations of Heart Surgery. A series of drawings was prepared demonstrating the attachment of a prosthetic mitral valve between the left atrium and left ventricle of the heart and describing the appearance and function of the valve in place. This is the first time that a mitral valve has been duplicated in structural form with synthetic materials and attached in place with successful results. The drawings and valve were both developed by the Medical Arts Section.

Illustrations of Temporal Lobotomy. A series of operational plates were prepared for NINDB, demonstrating the left temporal lobotomy and accurately describing the anatomy exposed under this procedure.

Models of Embryo Brain. The first in a series of three-dimensional models of the embryo brain was produced for NINDB. The models are 16.5-times actual size and are laminated from wood slices, each slice being cut to shape from an enlarged tracing of a slice of the actual brain. Finished models will be used to study brain confirgurations which are too small for accurate measurement and study in their actual size.

Models of Hands. Moulages of the hands of patients under treatment for arthritis were prepared for NIAMD. They are being studied to determine anatomical changes occurring during treatment.

Plastic Splint. A new type plastic splint was developed for the Clinical Center Physical Therapy Section. The splint is made from a plastic sheet that can be warmed and molded over a plaster model of the affected joint. It is pliable and can be wrapped around the joint and held in place with cellophane tape or a built-in press-hold fastener. It is washable with soap and water, extremely light, has very little bulk, and can be reshaped if the joint changes form.

Heart-valve Molds. Plastic-metal molds of heart valves were developed for NHI. They are custom formed to meet the requirements of individual patients. The valves made from the molds have been used as replacements for human valves in several NHI patients.

Corrosion Specimens. A series of injection-corrosion specimens were prepared for NIAMD. The arteries and veins in the elbow region of monkeys (in progressive stages of flexion) were filled with colored plastic which set after filling the blood-flow cavities. The arms were then immersed in solution that digested the tissue, leaving the plastic venous system in position around the bone structure. The specimens are being used to study the stretch accommodation of arteries and veins.

Drafting. The Section's Drafting Unit completed 6,295 charts, graphs, maps, diagrammatic and technical illustrations in 1960, an increase of twenty per cent over 1959. The Unit continued to provide consultation and advice to

DRS, Medical Arts and Photography Branch, cont'd:

"part-time draftsmen" who are employed in Institute laboratories in other capacities but who work informally on charts and graphs to avoid the scientists' having to wait several weeks for drafting work because of the heavy workload in the Drafting Unit. Requests for charts for administrative use increased in 1960 and will probably continue to increase with the growth of NIH. Approximately seventy-five large color charts were prepared for presentation on NIH budget, space, staff and organization, and for other administrative purposes.

PHOTOGRAPHIC SECTION

In 1960 the Photographic Section completed 9,234 requests for services, an increase of 1,669 over 1959. Much of the increase is attributable to the application of photographic services to new program areas.

Production Figures for 1960

TABLE I

Incoming Requests	B&W Negs.	B&W Prints	B&W Slides	Color Slides & Transp.	Photo-stats	Motion Picture
9,234	34,177	149,915	28,634	20,981	42,341	24,026 ft.

The total number of negatives, color slides, and transparencies produced in 1960 is less than the number produced in 1959. However, this decrease reflects improvements in production methods and finished items for the requestors rather than a drop in the Section's productivity. Concerted study by the photography staff of production problems and the application of more efficient methods resulted in fewer rejects of highly critical results. The application of better instrumentation, across-the-board standardization of similar operations, and the more efficient use of film, both black-and-white and color, were also contributing factors.

The total black-and-white print output increased approximately 12 per cent over 1959.

Direct Processing Assistance for Research Personnel

TABLE II

Requisitions: (Submitted Negatives)	Requisitions: (File Negatives)	Processed: Black & White	Processed: Color	Processed: X-ray	Processed: Chromatograms
/1053/	440	/223/	/210/	206	45

The boxed-in figures represent the number of requisitions submitted requesting prints from negatives produced in research laboratories. A high percentage of these are of research material which must be custom printed, usually in consultation with the investigator. In many instances the investigator is present in our darkroom for several days while these prints are produced.

In addition, several personnel are trained and assigned to specific investigators to work out photo-printing problems. This is now an important function of the Section and demonstrates the fact that, although much photographic work is decentralized throughout the laboratories of NIH, scientists rely upon the Photography Section for certain technical functions that can be most effectively accomplished centrally. In addition, during 1960, 223 requisitions for black-and-white film were processed, many of which required special attention and involved consultation with the investigator to determine methods of exposure, types of film, etc., to be used in the laboratory. There were 210 requisitions in the past year for processing color films. This is a growing photo service that requires a close working relationship between the photo staff and the scientists utilizing photography in their own laboratories.

Significant trends occurring in the Photo Section involve methods and instrumentation. The section is now utilizing smaller cameras and roll films in lieu of more costly 4 x 5 cameras and sheet film for many general assignments. This has been made possible by technical developments in cameras and sensitized materials. Although it has required substantial training of photographers, the advantages in terms of economy and better photographic results are worth this effort.

Training. Considerable attention was given to the need for training within the Section in the fields of general photography, photomicrography, motion pictures, and personnel management. Internally, courses were set up in the fields of photomicrography and motion pictures, and a weekly training schedule arranged for approximately ten members of the staff. The unit chiefs of the photomicrography and motion picture specializations have set aside an hour each week to conduct the classes. Members of the photographic staff have also been selected to attend courses which will extend their experiences and basic knowledge into broader activities.

Patient Photography. There were 672 requests processed in this area. One series, as a typical example, required close collaboration with the Ophthalmology Department. This included a series of extreme close-up photographs of the eyes, culminating in a series of dark adaptation studies on approximately ten patients. Another example, an extensive series of studies in Endocrinology, included a complete follow-through of pre-operative, exploratory surgery, and post-operative photographs.

Much of this work in 1960 was done with the roll film cameras, thus cutting costs of film and giving certain physical advantages in the taking of photographs. Methods of standardization of exposure in black-and-white and color photography have been developed and are being used by all photographers working with patient photography.

Photomicrography and Gross Pathology. Photomicrography was used during the past year to produce 3,683 photographs, approximately three-fourths of which were made in color. The use of color film in this area has constantly increased. There were 1,291 gross specimen photographs made. These were evenly divided between color and black-and-white. The production of 677 photographs

of agar plates represents a significant increase. Although techniques in this field are still being refined, investigators have commended the manner in which the technical problems involved in this type of photography are handled at NIH. The end product is transient and unpredictable, so that the photography is conducted with the investigator present, and is done on verbal request and upon immediate notice to the Photographic Section.

Motion Picture. Although the Section's manpower and facilities for producing motion pictures are rather limited, more than 60 individual requests were processed. A short list will indicate some of the outstanding examples:

1. Studies on polio vaccine on experimental monkeys, for Dr. Gerald S. Borman, Lab. of Viral Immunology, DBS.

2. Studies on Minamata disease on experimental animals, for Drs. Kurland, Tolgay, and Faro, NINDB.

3. A series of informational motion pictures for Dr. Sanford Rosenthal, Chief, Lab. of Pharmacology and Toxicology, NIAMD, of burn shock experiments to be used for the Johns Hopkins TV show.

4. Cooperation with the surgical staff at Freedman's Hospital in photographing three prostatic cancer cases.

5. Studies of the turtle heart and alligator heart, for Dr. Glenn Morrow, NHI.

6. Techniques demonstrating surgical procedures used in dissecting spinal cords of the cat, for Dr. Karl Frank, NIMH.

7. Studies involving 18 patients displaying involuntary movements, for Dr. John Van Buren, Surgical Neurology, NINDB.

8. Post-operative studies of neurology patients for Drs. Joseph Adamkiewicz and Anatole Dekaban, NINDB.

9. Studies of six dogs used in experiments on drug effects on the neurological system, for Dr. Harriet Maling, NHI.

10. Assistance in producing the Clinical Center Information Office motion picture for recruitment of volunteers. In this instance the motion picture unit edited approximately 2,500 feet of film-clips and did initial shooting of approximately 1,000 additional feet.

One of the finest technical achievements was accomplished for NINDB. This project required close collaboration with the investigator in producing color film showing the injection and selective spread of fluorescein in the arterial and venous system in the cat brain. The picture was photographed at twelve frames per second with ultraviolet illumination only, and clearly shows how the dye concentrates in a lesion area.

Color footage was produced of human and bovine hearts in action on a pulse duplicator. It consists of close-ups showing the action of artificial and natural aortic and mitral valves and provides opportunity for study of heart valve action. The motion picture unit produced hot-press titles and provided the titling, editing and sound recording for these projects.

One project begun for the Ophthalmology Branch, NINDB, involves the use of a specially developed technique for photographing pupillary changes in approximately 100 patients. This is a continuing program involving "on call" photography of incoming patients and referral cases in order to produce a catalog of pupillary pathologies for the investigators in the field. The project was undertaken in September as a pilot study and has developed into an intensive research project which is expected to continue for approximately one year.

Informational Photography. There were 1,020 requests for informational photographs in the last year. These included 158 requests for photographing of visitors and 40 group photographs. Many of the visitor photographs were made on extremely short notice. Several major assignments were handled, including the dedication of the new DBS building by the King and Queen of Thailand, and the visit of high-ranking Russian officials to NIH. As in the past, most of the information photographs were requested for use in news releases, exhibits, and brochures and other publications.

Problems, Changes, Improvements

Changes in Branch Name, Organization and Functions. The Medical Arts and Photography Branch was given its present organization and functions in December, 1960. Its two sections, the Medical Arts Section and Photographic Section, were formerly part of the Scientific Reports Branch, DRS, which also included a Library Section, an Editorial Section, and a Publication and Reports Section. Late in 1959 it was decided that the editorial and publications and reports functions of the Scientific Reports Branch could better be provided through the NIH Office of Research Information. As a result, the Editorial Section and the Publication and Reports Section were transferred to ORI in January 1960. Meanwhile, it had also become evident that the NIH Library required more flexibility and a greater recognition of its importance to the NIH research community than were possible under its status as a section. Consequently, the Library Section was elevated to branch status in April 1960.

By April of 1960, then, the Scientific Reports Branch retained only its medical arts and photography functions and the branch name had become a misnomer.

For that reason, a formal request was made to change the branch name to the Medical Arts and Photography Branch. The request was approved in December.

MEDICAL ARTS SECTION

The increase in the Medical Arts Section's workload and staff has produced an overcrowded condition in the Building 10 space.

Plans were developed to improve the exhibit storage space in the sub-basement of Building 1. Plans were also made to move the Plastics Unit to the sub-basement of Building 1.

The Chief of the Section received a Superior Service award for his work on an exhibit for the Clinical Neuropharmacology Research Center, NIMH. Six employees of the Drafting Unit received a group award.

PHOTOGRAPHIC SECTION

Personnel recruitment and reassignment during the year improved the quality of the Section's services. A new position classification, Photographic Laboratory Technician, was established to facilitate the recruitment of well-trained personnel in this category. Formerly, a technician was first assigned to the darkroom, progressed to the status of assistant, and ultimately became a general photographer operating independently. The new Technician classification now makes it possible for an employee to make a career as a Photographic Laboratory Technician.

Two employees in the Office of the Section Chief received individual Superior Performance awards.

Serial No. 3.1
1. Med. Arts & Photo. Branch
2. Med. Arts Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Plastic molds for forming Heart Valve Prosthesis for Heart Surgery

Principal Investigator: Philip R. Joram

Other Investigators: Dr. Nina Braunwald

Cooperating Units: Surgery Branch, National Heart Institute

Man Years (calendar year 1960)
Total : .03
Professional: .03
Other : .00

Project Description:

Objectives: To develop a strong, durable, easily fabricated plastic mold for the casting of foamed plastic heart valve prosthesis to replace diseased valves during heart surgery.

Major Findings: The Plastics Unit technical and sample files were checked for materials and methods used in the plastics industry which would be applicable to this project. A material and a method were found. The material is a plastic steel consisting of 80% steel powder and 20% epoxy resin. It is a heavy liquid. A catalyst is added to the liquid and the mixture thoroughly blended. The material sets to a strong, durable mass in approximately one hour. The method is as follows: A plaster cast of the shape of the heart valve prosthesis is supplied by the heart surgeon. The cast is placed in a form to contain the plastic steel. It is lubricated with a separating medium and the plastic steel mixture is poured over the cast, within the retaining walls of the form, to completely cover the plaster cast. The plastic steel is allowed to harden. The cast is removed from the hardened mold. The mold is replaced in the form, a separating medium is applied to the surface of the cavity left by the cast, and more plastic steel is poured. When set, the two parts are separated, giving a two-part positive-negative mold. The molds (26) have proved successful in forming plastics to make heart valves. Two such valves have been placed in heart patients and reported in the literature.

Part B Included Yes_____ No X

Serial No. 3.2
1. Med. Arts & Photo Branch
2. Med. Arts Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Simplified Plastic Wrist Splint for Physical Therapy Use

Principal Investigator: Philip R. Joram

Other Investigators: Dr. David Fried, Mrs. Vida Jo Niebuhr

Cooperating Units: Rehabilitation Department, Clinical Center

Man Years (calendar year 1960)

Total	:	.008
Professional:		.008
Other	:	.00

Project Description:

Objectives: To develop a simple, light weight, easily fabricated plastic wrist splint to immobilize a patient's wrist movements in physical therapy.

Major Findings: The Plastics Unit technical files and sample files were checked for appropriate materials and techniques used in the plastics industry which would be applicable to this project. Both a material and a method were found. From our material file and samples donated by a manufacturer a satisfactory splint was devised. The method was as follows: A plaster cast of the patient's wrist was supplied by the Rehabilitation Department. A pattern was made from this, using a special styrene-rubber plastic sheet with flocking on one side. This sheet was cut to shape from the pattern. An electric hot-air heat gun, similar to hair drying guns, with a temperature range of 300° - 500° F, was used to soften the plastic so that it could be manually formed around the plaster cast. This technique requires no special knowledge or training and is simple enough to be used by the personnel of the Rehabilitation Department.

Part B

Included Yes____ No X

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS - 4
Serial Number

2. LABORATORY AIDS BRANCH
Branch

3. Dr. Preston Holden
Branch Chief

Objectives

To provide in the most efficient and economical manner possible to the various Institutes and Divisions of NIH a number of essential research services that are best carried out on a centralized basis. These include animal production, quarantine, conditioning, treatment, surgery, and long-term holding services; the prevention and control of animal diseases; and bacteriological and tissue culture media, sterile glassware, and cagewashing services.

Programs

The provision of quarantine, holding, treatment, surgical and radiological services for the larger research animals, i.e., dogs, cats, monkeys, sheep, goats, horses, cattle, etc.

The production of high quality laboratory animals for research, including inbred strains and other special types.

Continuing surveillance, diagnosis, and investigation of the diseases of both large and small laboratory animals, and the development and application of disease prevention and control measures.

The production of all types of bacteriological and tissue culture media required in volume by NIH scientists.

DRS, Laboratory Aids Branch, cont'd:

The washing, sterilizing and processing of NIH laboratory glassware, and provision of cage washing services for the Clinical Center.

Progress and Accomplishments

Major effort was made during 1960 to bring LAB plans for staff, facilities and operations into line with the rapidly changing and expanding research needs of NIH. Acquisition of the NIH Farm made possible for the first time the design of adequate facilities for large farm animals. Also, it permitted planning to relieve the acute shortage of space for the quarantine and conditioning of dogs and cats.

In recognition of the need of NIH laboratories for research animals of more precise microbiological status, plans were revised during 1960 for the remodeling of Wings F and G (T-18 and T-19) Building 14, to allow production of germfree and specific pathogen-free animals. Long-range plans associated with this were made for increasing and strengthening the staff of the Comparative Pathology Section to provide essential services in virology and bacteriology.

An LAB Safety Committee was organized, and all areas of Laboratory Aids operations at NIH-Bethesda were formally inspected during the year for hazardous conditions and operations.

During 1960, a more effective program for testing and reporting on lots of laboratory chow destined for NIH was worked out with the Ralston Purina Company. The tests are designed to assure freedom of the feed from any significant amount of estrogen-like substances that might have adverse effects on the rat and mouse colonies.

Early in November, the Branch was host to the deans of veterinary colleges and the heads of departments of veterinary science in land grant colleges.

A new Assistant Chief, Dr. Joe W. Atkinson, reported March 1, 1960. He participated in the Second National Conference on Evaluation in Public Health, Ann Arbor, Michigan, September 12-14, as a member of the Environmental Health Special Task Force. He is also President-elect of the Conference of Public Health Veterinarians.

DRS, Laboratory Aids Branch, cont'd:

Formal training of some type was provided for many employees. Although modest in nature, this program contributed noticeably to working efficiency. A series of training seminars was conducted for animal caretakers. Seven persons attended the Division's training course for supervisors, and three attended a USDA Graduate School evening course on "Basic Principles of Laboratory Animal Care." One staff member enrolled in a course in clinical diagnostic bacteriology, another took courses in calculus and statistics, and two enrolled in a chemistry course under the USDA graduate training program. The Animal Hospital Section cooperated with the D. C. Academy of Veterinary Medicine in conducting a 4-day course in canine neurology. Staff veterinarians attended or participated in the course, and in others at the Communicable Disease Center-PHS and the Armed Forces Institute of Pathology. The veterinary CO-STEP students attended formal sessions throughout the summer in addition to on-the-job training they received in the Animal Hospital Section.

Talks were presented and papers were published as follows:

"A rapid method of grafting skin on tails of mice," paper by Dr. D. W. Bailey and B. Usama published in Transplantation Bulletin, 7: 424-425, 1960.

"An automatic drinking fountain for dogs," paper by Dr. W. I. Gay and J. Carter published in Journal of the American Veterinary Medical Association, 137: 550-552, 1960.

"Attempts at replacement of the midthoracic esophagus with a gastric tube," a talk by Dr. L. F. Rubin at the Joint Meeting of the D. C. Academy of Veterinary Medicine and Region I of the American Hospital Association, Shoreham Hotel, Washington, D. C., February 25.

"Cultural and serologic studies on four dogs inoculated with two leptospiral serotypes, Leptospira pomona and Leptospira canicola," paper by Drs. R. W. Menges, M. M. Galton, and R. T. Habermann published in American Journal of Veterinary Research, 21: 371-376, 1960.

DRS, Laboratory Aids Branch, cont'd:

"Dysentery, tuberculosis and pneumonia of rhesus monkeys," a talk by Dr. R. F. Kinard at the CO-STEP seminar, NIH, in August.

"Etiology and prophylaxis of chronic respiratory disease in rats," a talk by Dr. C. W. McPherson at the Helminthological Society of Washington, March 25.

"Four internal parasites of monkeys: Nochtia nochti, Gastrodiscoides hominis, Anatrichosoma cutaneum, and Sarcocystis sp.," a talk by Dr. A. M. Allen at the Helminthological Society of Washington, March 25.

"Increasing the research value of laboratory animals through breeding practices," paper by Dr. D. W. Bailey published in Proceedings of the Animal Care Panel, 10: 117-122, 1960.

"Indirect ophthalmoscopy in veterinary medicine," paper by Dr. L. F. Rubin published in Journal of the American Veterinary Medical Association, 137: 648-651, 1960.

"Laboratory animal medicine," a talk by Dr. C. W. McPherson at the Communicable Disease Center biennial Conference for Public Health Veterinarians and Teachers of Preventive Medicine.

"Occurrence of inclusion bodies in viral diseases of man and other animals, and the susceptibility of laboratory animals to some of these diseases," paper by Dr. R. T. Habermann, F. P. Williams, Jr., and G. L. Fite published in Journal of the American Veterinary Medical Association, 137: 161-176, 1960.

"Occurrence of the nematode, Anatrichosoma cutaneum, in the nasal mucosa of Macaca mulatta monkeys," paper by Dr. A. M. Allen published in American Journal of Veterinary Research, 21: 389-392, 1960.

DRS, Laboratory Aids Branch, cont'd:

"Problems in laboratory animal medicine and animal care," a talk by Dr. P. Holden at the Communicable Disease Center biennial Conference for Public Health Veterinarians and Teachers of Preventive Medicine.

"Public relations," a talk by Dr. W. I. Gay at the Animal Care Panel meeting, St. Louis, Missouri, October 24.

"The determination of heterogeneity of inbred strains," a talk by Dr. D. W. Bailey at the Armed Forces Institute of Pathology course, Pathology of Diseases of Laboratory Animals, September 26-30.

"The transfer of rhesus monkeys from India to laboratories in the United States--the problems, causes of death and possible corrections," a talk by Dr. R. F. Kinard at the Armed Forces Institute of Pathology course, Pathology of Disease of Laboratory Animals, September 26-30.

"The use of trichloroethylene and halothane anesthesia in the restraint of laboratory primates," paper by Drs. R. F. Kinard and C. W. McPherson published in American Journal of Veterinary Research, 21: 385-388, 1960.

"Three important parasitisms of rhesus monkeys--pulmonary acariasis, strongyloidosis, esophagostomiasis," a talk by Dr. R. F. Kinard at the Helminthological Society of Washington, March 25.

"Two methods for coloring mast cells of mammalian tissues," paper by Dr. A. M. Allen published in American Journal of Clinical Pathology, 33: 461-469, 1960.

"Use of chicks for detecting Western Equine and St. Louis Encephalitis viruses in mosquitoes," paper by Dr. P. Holden, G. Solomon, and J. S. Blackmore published in American Journal of Veterinary Research, 21: 1078-1082, 1960.

DRS, Laboratory Aids Branch, cont'd:

"Veterinary medicine as a career," a talk by Dr. W. I. Gay at Paul Junior High School, Washington, D. C., February 17.

ANIMAL HOSPITAL SECTION

Construction is a very vital part of the Animal Hospital Section's program of caring for an expanding experimental animal population. Although no major construction was possible in 1960, minor remodeling and relocation of activities provided additional office and storage space at NIH-Bethesda. A 15-acre pasture was fenced, a cattle and goat shelter erected, and temporary pens and outdoor houses for 48 dogs were constructed at the new NIH Farm. Conversion of facilities allowed the housing of seagulls in one room of Building 28, NIH, and the holding of two additional horses at the Rockville Farm.

The Chief of the Section visited a number of research centers in eastern United States to review various types of housing and care for large laboratory and farm animals, and cooperated with the Research Facilities Planning and Plant Engineering Branches in planning renovations and new construction for the NIH Farm.

More than 150 persons visited the Animal Hospital Section during 1960; many were from other agencies and research institutions seeking information and advice on animal care facilities and procedures. In March, for example, Mr. George Larrick, Commissioner, Food and Drug Administration, and five of his assistants visited the Section to acquire information that would be helpful in planning housing for the dogs used in FDA toxicity studies and other investigations.

New sources were developed during the latter part of 1960 for the purchase of dogs and cats (about 75 of each a month) of better quality than those received from the regular NIH contractor. About 30 percent of the current supply now comes from such extra sources, a significant factor in view of the relatively poor quality of the regular supply.

Actions taken during the year to improve efficiency of operations included installation of an air conditioner on the animal van; conversion to the use of screw-topped clysis bottles

for sheep blood; maintenance of all healthy dogs (except post-operative cases or those scheduled for surgery) on an economical dry dog-food diet; a concentrated, regularly scheduled insecticidal program in Building 14; and revision of the Section's filing system to dispose of approximately 3 cubic feet of outdated material.

The professional staff of the Section conducted or cooperated in a number of research projects concerned with various aspects of experimental surgery, etiology and pathogenesis of bovine ocular squamous carcinomas, contrast radiography, and dysentery in monkeys. In addition, an evaluation was made of some 550 monkeys purchased from Primates, Inc., and of monkeys regularly obtained through Okatie Farms; those from Primates, Inc., a more economical supply source, had a higher rate of respiratory infections but the mortality rate was essentially equivalent. This information was provided the Division of Biologics Standards, the primary purchaser of monkeys at NIH.

The Section continued its highly effective cooperation with humane groups and national organizations concerned with animal resources and care, in medical research. The Chief and a member of the Section presented a number of papers and talks before professional groups. An excellent exhibit on retinal diseases of the dog and cat was displayed at the annual meeting of the American Veterinary Medical Association.

Four veterinary officers joined the staff during 1960. One veterinarian transferred to the Comparative Pathology Section of the Laboratory Aids Branch; one left for post-graduate training; and one was released to gain experience in germfree animal production techniques, preparatory to initiation of the germfree unit proposed for the Laboratory Aids Branch.

Blood and urine of animal origin were furnished the Institutes by the Section in the following amounts:

DRS, Laboratory Aids Branch, cont'd:

Animal	Blood	Urine
Sheep	99 liters	200 cc
Horse	29.4 liters	200 cc
Cattle	6 liters	200 cc
Dog	550 cc	500 cc
Goat	500 cc	--
Monkey	70 cc	100 cc
Cat	50 cc	4000 cc

Approximately 300 surgical procedures were carried out by the Experimental Surgery Unit, either in conjunction with or as a service to investigators from the Institutes. X-ray procedures totalled 310, with 869 films developed.

A total of 673 long-term animals were treated at various times during the year. The average number of animals on long-term holding at NIH-Bethesda was 297; at the Rockville Farm, 154; and at the NIH Farm, 44. A number of farm animals, as well as six seagulls, were procured and transported in response to requests from NIH investigators. For example, 12 Merino sheep, rare in eastern United States, were obtained for the National Heart Institute. Tentative receipt and issuance data on dogs, cats, and monkeys follow:

	Received	Death Rate	Issued
Dogs	4490	1.26%	4350
Cats	2904	14.2 %	2466
Monkeys	3138	9.94%	2378

ANIMAL PRODUCTION SECTION

A substantial number of the animals issued by this Section to meet the special requirements of various NIH laboratories were pregnant or newborn animals, animals with "naturally" occurring tumors or other abnormalities (e.g., glaucoma in rabbits), and animals produced by special matings. Approximately 300,000 inbred mice, rats and guinea pigs, and 224,000 NIH "Brother X Sister" mice were issued during the year. High quality was maintained in all categories of animals produced.

DRS, Laboratory Aids Branch, cont'd:

Nutrition research continued, with the initiation of a study comparing six types of diets for mice and rats. Other studies concerned bedding materials, mating systems, foster nursing, production records, the value of reducing rabbit litters at birth to a standard number, and environmental factors as a source of estrogen-like stimulation in mice. In cooperation with an NIAID investigator, the development of a colony of rabbits with specific gamma globulin characteristics has been undertaken.

Production was adjusted in several strains of animals to more closely meet NIH needs. In spite of increased wage rates for animal caretakers, prices were reduced on several categories of animals.

A temporary reduction in number of rabbits available for issue, resulting from concentrated efforts to remove all coccidia-infected animals, was successfully compensated for through carefully planned purchases from outside sources.

A comparison of total animal production for 1960 with that of 1959 and 1958 shows an increase of 8.2 percent over 1959.

	1958	1959	1960*
Mice	794,000	839,096	904,392
Rats	156,000	165,353	180,263
Guinea Pigs	27,200	27,996	27,923
Rabbits	10,800	11,826	11,829
Hamsters and other species	23,700	31,377	39,911
Totals	1,011,700	1,075,648	1,164,318

* Estimated

The Section assisted the various NIH laboratories in obtaining salvaged caging equipment; $14,625 worth of cages were issued from the used-cage pool.

Net man-hours worked increased 1.8 percent from 167,633 in 1959 to 170,625 in 1960.

DRS, Laboratory Aids Branch, cont'd:

GENETICS UNIT

In general, the primary mission of providing adequate numbers of genetically controlled breeding stock to the Inbred Production colonies was successfully fulfilled by the Genetics Unit, which had more efficient operation in 1960 than in past years, in terms of material costs, man-hours and animal health.

The production rate in the mouse colonies has risen steadily since April 1959. The present level of efficiency, as measured by the number of mice weaned per female breeder each week, is 40 percent greater than in 1959. This increase enabled the Unit to reduce the number of breeders maintained in the Inbred Nucleus Colony from 1,600 to 1,200.

Mouse infantile diarrhea has ceased to be a major problem in the Inbred Nucleus colonies, with only one percent of the litters having diarrhea in the diarrhea-prone BALB/c and C3H colonies. The incidence has remained low throughout the year and has shown no seasonal fluctuations. Elimination of the problem is attributed to the improvements in animal care, consisting primarily of more frequent cage changes, litter reduction, and optimal nutrition.

Pending provision of more efficient water tubes (a non-drip type, now being tested), the inbred guinea pigs receive their water supply through a daily allotment of vegetables. An apparently healthier guinea pig is now being produced in this dry environment and no unexpected deaths have occurred since the inauguration of this change in care procedure.

Genetic homogeneity of NIH inbred mouse strains is now being continually checked by routine skin-graft tests. One female from every first litter produced by a breeder in the Expansion colony serves as a donor of skin to be transplanted onto a Foundation colony (pedigreed) ex-breeder female of the same strain. Any heterogeneity due to errors in the mating regimen or due to mutations at the histocompatibility loci occurring with the Inbred Nucleus colonies will be detected by this testing procedure. This gives added assurance to investigators that they are receiving animals of purported genetic purity.

DRS, Laboratory Aids Branch, cont'd:

As an aid to NIH investigators, a listing of species, stocks and strains ("Stock List") maintained in the Animal Production Section has been reproduced and distributed to users of laboratory animals throughout the reservation. Each animal type is described according to its known genetics, its origin and its known morphological and physiological characteristics. This list should prove to be quite helpful to the research investigator in selecting the animal type that will be the most advantageous for use in his work.

Concurrently with the distribution of the "Stock List," a service to develop new strains with unique traits for augmenting research efficiency is now available. New characteristics that are genetically determined must be developed from a population of animals which is genetically heterogeneous, since variability is the raw material from which a new trait can be molded through artificial selection procedures. A highly heterogeneous population for these ends will be established from a double-hybrid cross of strains DBA/2, A/He, C57BL/6 and BALB/c. We are currently getting litters from matings of the fifth hybrid generation. These selection experiments are aimed at providing the NIH investigator with experimental animals of even greater effectiveness.

COMPARATIVE PATHOLOGY SECTION

In carrying out its primary responsibility to provide diagnostic and disease control services for the animal colonies maintained by the Animal Production and the Animal Hospital Sections, the Comparative Pathology Section performed various kinds of examinations on over 10,000 animals during 1960. A limited number of parasitology, bacteriology, mycology, hematology and urine examinations were performed. A large number of autopsies were performed on a variety of animals, as indicated below:

Mice	9,654
Rats	1,853
Guinea pigs	1,287
Rabbits	530
Monkeys	114
Dogs	48
Cats	18
Farm animals	7

Disease control work was directed primarily against coccidiosis in rabbits, ectromelia in mice, and tuberculosis in monkeys. All available evidence indicates that each of these control programs has been successful within the limits of the objectives set forth by current program design. See individual project reports.

Individual research projects included studies of chronic respiratory disease of rats, bladder stones of mice, filariasis of dogs and monkeys, respiratory diseases of cats, and diseases of monkeys during transport.

MEDIA AND GLASSWARE PREPARATION SECTION

In both media and glassware preparation, the trend of previous years continued and record production figures were reached in 1960. In the Media Unit, there was approximately a 5.2 percent increase in requisitions over 1959, for a total of almost 8,500. About 5,350,000 pieces of glassware were processed, representing a 7 percent increase over 1959. The cage washing team handled 400,000 pieces, essentially equal to last year's total.

Plans for improvement of glassware services call for the installation of a permanent sorting area for glassware, with stainless steel shelves and tables; installation of an ultrasonic glassware washer; increased deionized-water pressure for the pipette washers; relocation of deionizers to allow direct control of water quality by personnel of the Unit; and purchase of new glassware washing baskets.

Problems

Primary problems are those associated with budgeting and staffing to adequately meet needs of the Institutes. There is need for better information sufficiently in advance of increases or shifts in emphasis among the various research programs to anticipate corresponding demands for expanded or revised services from the Laboratory Aids Branch.

It is more efficient and economical to prepare in advance, and be ready to meet needs as they develop. This usually requires

several years for planning, constructing or remodeling, and equipping buildings; and from six months up to a year or more for recruiting and training personnel, particularly key professional staff.

Even though it is extremely difficult at times to gain approval of an adequate budget for a "service" operation before a crisis actually develops, nevertheless, with facilities overcrowded (a chronic condition up to this time), and with a bare minimum of experienced personnel, it is often difficult or impossible for LAB to maintain on-going activities at the proper level; it is even more difficult to meet requests from investigators for new or special services.

Budget

Again in 1960, the monthly allotment for purchase of glassware was entirely inadequate, and did not permit us to keep stock levels above minimum requirements. Moreover, the cost of glassware continues to rise. The squeeze between increasing demands for glassware and an allotment which has not been increased since 1956 produces repeated shortages and complaints.

The Comparative Pathology Section is currently operating on a budget insufficient to match the cost of the services which it should provide. The situation is extremely unfortunate in view of the complex and critical nature of the responsibilities carried by this Section.

Because of the rapid growth of the animal colonies during the last five years, these responsibilities have become increasingly difficult to fulfill. During 1960, the Animal Production Section produced over 1,150,000 animals and the Animal Hospital Section quarantined more than 10,000 animals. Yet the Comparative Pathology Section had only four professional men to detect, identify, and control laboratory animal diseases.

Recent experiences have shown that the control of outbreaks of certain diseases of laboratory animals constitutes major crises in terms of manpower for this Section. To effectively administer control and eradication programs for the

coccidiosis outbreak in rabbits and the ectromelia outbreak in mice during 1960, it was necessary to shunt manpower to these programs from other disease control programs of the Section and from other Sections of the Laboratory Aids Branch.

At the present time, surveillance of the animal colonies is maintained primarily by employing methods of anatomical pathology and histopathology. While these methods have proved to be very practicable for determination by a small staff of investigators of the presence of diseases in the large NIH colonies, they should be supported by adequate diagnostic microbiology services. The need for such services becomes obvious when it is considered that approximately 90 percent of the deaths among quarantined animals are caused by infectious diseases. Furthermore, it is known that certain highly contagious diseases pose a constant threat to the colonies. Without microbiological testing, the Comparative Pathology Section is poorly prepared to make positive identification of such diseases, a factor which could cause serious delay in the initiation of control procedures.

Furthermore, Laboratory Aids Branch is making plans for the production of "germfree" and "specific pathogen-free" animals. If the Comparative Pathology Section is to service such a program, it will be essential that microbiologists, well-trained in virology as well as in bacteriology, be added to the staff. It is proposed to strengthen the staff and expand the facilities of this Section to a level more commensurate with its responsibilities. This action will be initiated in FY 1962, and carried forward as swiftly as resources permit.

Personnel

Good personnel management has been somewhat hampered by the slowness of personnel actions. The delays encountered in requests for promotions and for reviews of records and advice in disciplinary cases have been frustrating.

The quality of people available for hire as new animal caretakers has been fair to poor. As a result of careful selection and supervision, all caretakers hired within the past year have

performed fairly satisfactorily and several show potential for becoming quite proficient. However, to hire and retain the kind of personnel needed, wages for supervisors and the top group of caretakers must be increased.

The overall increase in production of media and glassware during 1960 was effected without increase in personnel. However, there were times when shortage of help impaired the quality of services rendered.

Mr. Melvin W. Bryant, an employee of almost thirty years and Chief, Media Preparation Unit, for over 15 years, was recently found to have contracted tuberculosis. The loss of Mr. Bryant's leadership will adversely affect operations within that unit. In tissue culture media production, the present work force of three is seriously hampered by the absence of even one person. This situation occurs frequently during the year, due to vacations, sick leave and inclement weather. In addition, it is impractical to press for quantity of output per employee, since this would affect the quality of the media. If the necessary funds can be obtained, we will renovate and equip space, and employ the necessary personnel for a more adequate tissue culture production unit.

The glassware preparation unit is also seriously hampered by a shortage of personnel. During the latter part of 1960, there was a considerable amount of illness among employees of this unit. Some services were very adversely affected, i.e., pipette washing, cage washing, acid cleaning, etc. We plan to employ additional personnel in this Unit during FY 1962. It is hoped that pressures can be somewhat relieved by the purchase of a mechanical pipette plugging machine. The cost of this machine, expected to be about $1,000, will be offset by its labor-saving advantages.

Space for Production of Small Animals

The location of the mouse colony in Building 12 presents a continuing problem. Building 12 was originally used for animal production on a "temporary" basis, and is a poor physical facility for this purpose. The cage washing machine is not designed to wash stands and carts, and these articles must be washed by hand at infrequent intervals. The jars must be presoaked or the machine does not do a satisfactory job with them. The close

proximity of monkey-holding rooms and other service facilities is undesirable; LAB has no control over sanitation in these areas and the possibility of the introduction of infection is always present. It is difficult to restrict unauthorized personnel from the area. Ventilation and temperature control is inadequate, and the adverse effects of high temperatures during the summer months result in decreased mouse production. Also, the temporary wooden and plaster board partitions offer harborage for insects.

In addition to the undesirability of Building 12 for animal production purposes, there is a definite need for more space to reduce crowding, expand production sufficiently to alleviate chronic shortages in certain categories of animals and meet increased needs of the Institutes as they develop, and initiate production of germfree and specific pathogen-free (SPF) animals. It is expected that Wings F and G will be released for animal production during 1961. Wing F will be used for the production of conventional animals. This will house the mouse colony now in Building 12, and accommodate an increase in rabbit and hamster production. Part of Wing G will be used for production of SPF animals and part for production of germfree animals. Plans are now being developed for the necessary remodeling of these wings to be done in FY 1962. In addition, it is expected that two new animal production wings with service facilities will be completed on the NIH Farm in FY 1964.

Space for Monkeys

The shortage of space for the quarantine and long-term holding of monkeys continues. However, present plans call for enclosing the six large outdoor runs on Wing D, Building 14, during 1961. This will alleviate the situation to a considerable extent, until a new primate wing can be constructed at the NIH Farm in FY 1964. As another possible means of relief, poultry-type cages adapted for housing laboratory monkeys will be purchased for trial. If satisfactory for general use, these cages will reduce labor and housing costs and floor space required for primate quarantine.

DRS, Laboratory Aids Branch, cont'd:

Quality of Dogs and Cats

Under the FY 1961 dog and cat supply contract, a very high percentage of animals received became ill during the quarantine period. There has been some improvement recently, but an adequate number of dogs and cats of good quality are virtually unavailable to our investigators. This is due to the greatly increased use of dogs in medical research which has caused a competition for quality animals; the nature of the contractor's supply, which is apparently city pound animals held too long and not well cared for during holding periods; and our current lack of space to condition these inferior animals properly. There seems to be little hope that an adequate supply of dogs and cats of high quality will be obtainable from commercial contractors in the future.

As a short-term solution to the problem intensified effort will be made to obtain more animals from local pounds. It is planned to test the value of having animals vaccinated and conditioned at the pounds, from the first day they are received. In addition, a temporary dog and cat quarantine facility is to be constructed at the NIH Farm during 1961, to provide as soon as possible the necessary space for a longer period of quarantine and conditioning of animals received from commercial contractors.

Breeding colonies to produce dogs and cats for research purposes may be necessary in the near future.

Equipment

The Animal Production Section has only one truck for animal deliveries. When it is necessary for the truck to be serviced, it is almost impossible to get a substitute vehicle from the motor pool.

Aluminum animal transport cages will be purchased to improve the efficiency and capacity of the large animal van. However, an additional utility vehicle suitable for transporting large animals will be required by the Animal Hospital Section in 1961.

There is still no adequate storage of essential replacement parts for the glassware washers. The program of maintenance should include periodic checking for wear, etc., and a supply of replacement parts.

DRS, Laboratory Aids Branch, cont'd:

A steam cleaning machine is needed to enable adequate cleaning of the pit area under the cage washers in Building 10.

In Building 14, several months may elapse between the time a cage washer or part breaks down and the time when it is repaired. The basic trouble seems to be the inability to obtain repair parts on short notice.

Painting

The up-keep of physical plant, and the extent of deterioration or damage, is a matter of much concern to the occupying program. Accordingly, Laboratory Aids Branch requested the painting of numerous rooms and corridors in Building 14 in 1958, and again in 1959. No action was taken because such projects were included in "future plans." The animal wings have not been repainted since they were constructed in 1953.

Animal Diseases

Diseases in the animal colonies include respiratory diseases of cats, mouse infantile diarrhea, snuffles in rabbits, chronic respiratory disease of rats, and respiratory and enteric diseases of monkeys. In 1961, major emphasis will be placed on investigations and development of control measures for these infections.

Future Objectives

A major objective is to proceed with comprehensive planning for expanded facilities which will relieve present overcrowded conditions in the various Sections of Laboratory Aids Branch, and permit more orderly and efficient response to needs and problems as they arise. In conjunction with this, it is planned to strengthen the professional and semi-professional staffs, particularly in the Comparative Pathology and Media and Glassware Preparation Sections.

LAB is planning to initiate production of germfree and specific pathogen-free animals in 1962. Completion of renovations on existing buildings at the NIH Farm should allow moving all NIH farm animals from the Rockville Farm during the first half of 1961.

DRS, Laboratory Aids Branch, cont'd:

Throughout 1961, LAB will make a continuing review of operations (1) to identify existing or potential problem areas and carry out or recommend corrective actions, as may be appropriate; and (2) to provide improved, more efficient services wherever possible.

Attachment

(ATTACHMENT I)

Serial No. 4.1
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: CONTINUED STUDY IN CONTRAST RADIOGRAPHY

Principal Investigator: William I. Gay, D.V.M.

Other Investigators: Sara Jane Uhrich, D.V.M.

Cooperating Units: Staff, Animal Surgery Unit, A.H.A.

Man Years (calendar year 1960):
Total: .10
Professional: .05
Other: .05

Project Description:

Objectives: This study evaluates contrast radiography techniques as a means of demonstrating experimental surgical results without sacrificing the experimental animals.

Proposed Course of Project: Successful outlines of the ventricle of the brain of the dog have been made by Dr. Sara Jane Uhrich. Dr. Giovanni Di Chico, NINDB, has volunteered to assist in developing retrograde pneumoencephalography as a diagnostic technique in the dog.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.2
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: SURGICAL LENGTHENING OF LONG BONES IN THE DOG

Principal Investigator: William I. Gay, D.V.M.

Other Investigators: None

Cooperating Units: Staff, Animal Surgery Unit, A.H.S.

Man Years (calendar year 1960):
Total: .05
Professional: .02
Other: .03

Project Description:

Major Findings: The dogs used in this experiment have all been euthanized. The operated bones are being radiographed and sectioned for histopathological study. None of the grafting materials used in this experiment were useful in hastening the healing of defects in weight-bearing long bones. The results will be submitted to orthopedic experts for evaluation before publication of this work is proposed.

Part B included Yes____ No X

(ATTACHMENT I)

Serial No. 4.3
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: COMPLETE SURGICAL HYPOHYSECTOMY IN DOGS

Principal Investigator: William I. Gay, D.V.M.

Other Investigators: Dr. James O. Davis, NHI

Cooperating Units: Staff, Animal Surgery Unit, A.H.S.

Man Years (calendar year 1960):
Total: .02
Professional: .01
Other: .01

Project Description:

Major Findings: This study is complete and will be reported in the literature by Dr. Davis. It is still retained as a project because Dr. Gay is accumulating information about pituitary deficiencies in dwarf-like dog breeds to compare with hypophysectomized dogs used in this series. If the comparison is interesting, a paper will be written to describe this information to the veterinary profession.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.4
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: IMPROVED ANIMAL HUSBANDRY PRACTICES

Principal Investigator: William I. Gay, D.V.M.

Other Investigators: Mr. John L. Carter

Cooperating Units: Long Term Holding Unit, A.H.S.

Man Years (calendar year 1960):
Total: .05
Professional .02
Other: .03

Project Description:

Objectives: Techniques designed to improve the quality and efficiency of large laboratory animal care are evaluated.

Proposed Course of Project: An automatic feeding and watering system for dog kennels has been developed. During the past 12 months it has functioned very efficiently. Other methods of housing and feeding dogs, cats, and monkeys are being evaluated.

Part B included Yes X No

(ATTACHMENT I)

Serial No. 4.4

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications

Publications:

Gay, W. I., and Carter, J. L. An automatic drinking fountain for dogs. Journal of the American Veterinary Medical Association, 137: 550-552, 1960.

Honors and Awards related to this project:

None

(ATTACHMENT I)

Serial No. 4.5
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: COMPLETE REMOVAL OF THE PINEAL BODY OF THE DOG

Principal Investigator: Dr. James O. Davis, NHI

Other Investigators: William I. Gay, D.V.M.

Cooperating Units: Staff, Animal Surgery Unit, A.H.S.

Man Years (calendar year 1960):
Total: .02
Professional: .01
Other: .01

Project Description:

Major Findings: This experiment yielded negative data and the later operations were not uniformly successful. Dr. Gay will attempt several more operations. If they are successful, the technique will be described for publication; if not the project will be dropped.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.6
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: AN ABDOMINAL WINDOW FOR VIEWING THE VISCERA OF A RABBIT

Principal Investigator: Sara Jane Uhrich, D.V.M.

Other Investigators: William I. Gay, D.V.M.
Dr. Jan Cammermeyer, NINDB

Cooperating Units: Staff, Animal Surgery Unit, A.H.A.

Man Years (calendar year 1960):
Total: .15
Professional: .10
Other: .05

Project Description:

Objectives: The purpose of this project is to evaluate a lucite window for viewing the abdominal viscera of the rabbit.

Proposed Course of Project: The project was dropped by Dr. Jan Cammermeyer although favorable results were being obtained. It appears worthwhile for Laboratory Aids Branch to continue with the project.

Part B included Yes____ No X

(ATTACHMENT I)

Serial No. 4.7
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: TESTING OF CASTIPLAST 11, 17 and 327 (RESINS OF THE EPOXY TYPE) IN TISSUE

Principal Investigator: Sara Jane Uhrich, D.V.M.

Other Investigators: William I. Gay, D.V.M.

Cooperating Units: Staff, Animal Surgery Unit, A.H.S.

Man Years (calendar year 1960):
Total: .10
Professional: .05
Other: .05

Project Description:

Objectives: Pieces of Castiplast 11, 17 and 327 were implanted into animals (rats and dogs) to determine tissue tolerance. Mr. John F. DeBroske, of the Instrument Engineering and Development Branch, DRS, judged this to be useful for the manufacture of parts of the heart lung pump and for the use of prosthetic devices for bone replacement.

Proposed Course of Project: The Castiplast has not caused detectable tissue reactions. Histopathological examination must be made of these specimens. If the plastic appears to be inert in tissue then it will be evaluated for bone and other prosthetic devices.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.8
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: STUDY OF BOVINE OCULAR SQUAMOUS CARCINOMA

Principal Investigator: Dr. Francis Abinanti, NIAID

Other Investigators: William I. Gay, D.V.M.
Dr. Mearl Stanton, NCI

Cooperating Units: Staff, Animal Surgery Unit, A.H.S.

Man Years (calendar year 1960):
Total: .10
Professional: .05
Other: .05

Project Description:

Objectives: To determine if cancer eye of cattle is of virus etiology. To study the pathogenesis of the disease.

Proposed Course of Project: One hundred twenty cases of this disease are under study in the herd at Bay Manor Farms, Lewes, Delaware; operations have been performed on 28 animals and specimens removed for histological and virological study.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.9
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: RUMEN FISTULA PLUGS FOR GOATS

Principal Investigator: Sara Jane Uhrich, D.V.M.

Other Investigators: None

Cooperating Units: Staff, Animal Surgery Unit, A.H.S.

Man Years (calendar year 1960):
Total: .20
Professional: .15
Other: .05

Project Description:

Objectives: To design a plug for rumen fistulas in goats which will remain in place for several months and allow repeated removal of the rumen contents. This has been possible in sheep and cattle in the past but not in goats.

Proposed Course of Project: Different types of fistulas have been tried in order to overcome the problem of keeping the plug in place. A plastic assembled type now in use has been kept in place in the rumen fistula for three months.

Part B included Yes____ No X

(ATTACHMENT I)

Serial No. 4.10
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: BACTERIAL RESISTANCE TO MEDICATION IN MONKEY DYSENTERY

Other Investigators: Lt. J. A. Davies, U.S.N.

Cooperating Units: Primate Quarantine Unit

Department of Bacteriology,
Naval Medical Research Institution

Man Years (calendar year 1960):
Total: .10
Professional: .05
Other: .05

Project Description:

Objectives: Rectal swabs are cultured for bacterial sensitivity and identification of pathogens to determine if bacterial resistance is allowing monkeys to die in spite of routine medication.

Proposed Course of Project: Shigella sp., the primary cause of monkey dysentery, appears not to be resistant to the common antibiotics. However, Proteus sp. and some of the other enteric organisms are resistant to eight to ten of the common antibiotics. It is possible

Part A (Cont'd)

that the pathogens may be killed off by antibiotics but the damage caused by the pathogens allows other bacteria to invade causing death of the animal.

Part B included Yes____ No X

(ATTACHMENT I)

Serial No. 4.11
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: THE EFFECT OF REPEATED SHIGELLA CHALLENGE ON MONKEYS

Principal Investigators: Cmdr. T. Floyd, U.S.N.

Other Investigators: H. G. Arm, Lt. Cmdr., U.S.N.
Lt. Jack A. Davies, U.S.N.
Carl E. Miller, D.V.M.

Cooperating Units: Animal Hospital Section, NIH
Department of Bacteriology,
Naval Medical Research Institute

Man Years (calendar year 1960):
Total: .07
Professional: .02
Other: .05

Project Description:

Objectives: Monkeys have been subjected to repeated challenges with approximately 1×10^9 Shigella organisms isolated from the monkeys with symptoms of dysentery in the NIH colony.

Part A (Cont'd)

Proposed Course of Project: No conclusive results to date. The Shigella has not consistently caused disease. This project is being continued to try to determine mechanism initiating Shigella dysentery.

Part B included Yes_____ No__X__

(ATTACHMENT I)

Serial No. 4.12

1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: EXPERIMENTAL PRODUCTION OF VITREOUS DETACHMENT IN DOGS

Principal Investigator: Dr. Edward Okun, NINDB
Other Investigators: Dr. Lionel F. Rubin, DRS
Cooperating Units: Ophthalmology Branch, NINDB

Staff, Dog and Cat Quarantine Unit, Animal Hospital Section

Man Years (calendar year 1960):

Total:	.14
Professional:	.07
Other:	.07

Project Description:

Major Findings: Experimental procedures are completed and are being evaluated.

One phase of this, "Retinal Breaks in the Senile Dog Eye" will be presented by Dr. Okun at the Eastern Section Meetings of the Association for Research in Ophthalmology, February 17 and 18, 1961 at NIH.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.13
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: INCIDENCE OF BLESSIG-IWANOFF CYSTOID DEGENERATION IN DOGS AND CATS

Principal Investigator: Lionel F. Rubin, V.M.D.

Other Investigators: None

Cooperating Units: Staff, Dog and Cat Quarantine Unit, A.H.S.

Man Years (calendar year 1960):
Total: .14
Professional: .07
Other: .07

Project Description:

Major Findings: This is included in a project which determines the prevalence rate of lesions of the canine fundus. The experimental portion of this survey has been completed, and awaits the results of evaluation.

Histopathological studies of three previously undescribed diseases are in progress.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.14
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: THERAPEUTIC APPLICATIONS OF PARTIAL PENETRATING KERATOPLASTY IN DOGS

Principal Investigator: Lionel F. Rubin, V.M.D.

Other Investigators: None

Cooperating Units: Staff, Animal Surgery Unit, A.H.S.

Man Years (calendar year 1960):
Total .14
Professional: .07
Other: .07

Project Description:

Major Findings: Experimental surgery is in progress. Twenty transplants have been attempted with varying degrees of success. The technique has not been perfected, especially with respect to postoperative care.

The principal investigator is on a fellowship at the University of Pennsylvania. He is continuing this work there.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.15
1. Laboratory Aids Branch
2. Animal Production Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: A COMPARISON OF SIX TYPES OF DIETS FOR MOUSE AND RAT PRODUCTION

Principal Investigators: Mr. Richard L. Pierson
Miss Damara Bolte'

Other Investigators: Charles W. McPherson, D.V.M.
Mr. John P. Warfield

Cooperating Units: None

Man Years (calendar 1960):
Total: .30
Professional: .15
Other: .15

Project Description:

Methods Employed: Six rations are being tested. Each ration is being fed to an equal number of breeding units in a strain of inbred mice, a strain of inbred rats, and general purpose mice. Other possible variables, such as position of animals on cage stand, are being controlled. The following factors are measured and recorded for each group of animals: amount of feed used, number of litters born, number of animals per litter, weaning age, number of animals weaned, average weight of offspring at weaning, and the condition of the animals at weaning.

Part A (Cont'd)

Proposed Course of Project: No evaluation of results of this project has been attempted since the project must run nine months before significant results can be obtained. The project started in May 1960.

Part B included Yes_____ No__X__

(ATTACHMENT I)

Serial No. 4.16
1. Laboratory Aids Branch
2. Animal Production Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: RESEARCH IN ANIMAL HUSBANDRY PRACTICES AND PROCEDURES

Principal Investigator: Charles W. McPherson, D.V.M.

Other Investigators: Mr. John P. Warfield
Mr. Richard L. Pierson
Miss Damara Bolte'

Cooperating Units: None

Man Years (calendar year 1960):
Total: .30
Professional: .20
Other: .10

Project Description: Research studies on housing, feeding, cleaning, breeding, sanitary procedures, etc., are an integral part of any production colony activities.

Objectives: During the past year the following subjects have been studied: the use of various bedding materials, the advisability of reducing rabbit litters to a standard number (8) at birth, the advisability of using foster mothers for certain rabbit litters, evaluation of a 1:1 mating system in the mouse colony, the value of keeping individual production records on guinea pigs, the value of foster nursing certain guinea pig litters, and evaluation of a forced breeding system in the guinea pig colony.

Part A (Cont'd)

Significance: The results of these investigations are quite interesting and in some instances will result in new procedures in the production colonies.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.17
1. Laboratory Aids Branch
2. Genetics Research Unit
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: DEVELOPMENT OF HISTOCOMPATIBILITY LINES DERIVED FROM TWO INBRED STRAINS OF MICE

Principal Investigator: Donald W. Bailey, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):
Total: .7
Professional: .5
Other: .2

Project Description:

Objectives: This project is a survey of the histocompatibility genes that determine the rejection of grafts exchanged between the strains BALB/c and C57Bl/6. A count will be made of the loci at which these differences are determined and as many as possible will be assayed for the effect that each has upon the survival time of a graft.

Methods Employed: There are two lines of attack. The first is to have an array of 24 inbred lines, now in the 7th generation, which were derived from a hybrid cross of BALB/c and C57Bl/6 strains. These lines are being maintained by full-sib matings; however, in each generation a choice is made as to which of two sisters will be mated on the basis of the

Part A (Cont'd)

survival of their skin grafted on the brother to which one of them is to be mated. This system of combined selection and inbreeding is designed to speed up the inbreeding process. The investigator expects the genes to become randomly dispersed throughout these lines and to become fixed, as a consequence of the inbreeding. The percentage of surviving C57Bl/6 and BALB/c grafts placed on crosses of these lines will enable a determination to be made of the number of genes fixed in each of the lines and the parental-strain source of those genes. Through various hybrid combinations of these lines, the investigator expects to be able to limit the genic difference (compared to one of the parental strains) to about any one desired for individual attention.

The second line of attack utilizes a series of backcrosses, originating from the same two inbred strains, BALB/c and C57Bl/6, and should prove to be more effective than the system proposed above. Backcrosses consistently made to the BALB/c strain, say, will gradually dilute out the number of C57Bl/6 genes. In fact, individuals of the third backcross would be expected to be heterozygous on the average, for C57Bl genes at 1/8 of their loci. If there were but eight local differences between the parental strains, then the investigator would expect on the average, that each individual would posses but a single gene difference from the BALB/c strain. The number would of course vary, but nevertheless, by appropriate tests, e.g. grafting BALB/c strain skin on offspring of these third backcross individuals mated *inter se*, the number of gene differences could be ascertained and individuals with single gene differences could be selected for continued maintenance. Once lines are established with but single gene differences, then the investigator is in an excellent position to analyze gene effects singly and in combination.

Major Findings: The project is in the beginning phase. No major findings have developed.

Part A (Cont'd)

Significance: A major proportion of the research carried out on the inbred strains of mice, especially in NCI, revolve about the histocompatibility of tissues. Also a major portion of control of the genetic purity of the strains depends upon the genetics of histocompatibility. In tissue transplantation too great a reliance is placed on what is at present only assumed to be true. It is hoped that this work will answer such questions as: Do H-genes act additively or independently; or does it depend on which ones are dealt with? Moreover, since only three H loci have been isolated and studied in the mouse, the development of lines possessing some of the other loci should prove of interest to students of tissue transplantation.

Proposed Course of Project: The lines that are to be established will be maintained for further studies on association with disease, linkage studies and transplantation.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.18
1. Laboratory Aids Branch
2. Genetics Research Unit
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: EFFECTS OF INBREEDING ON RELATIVE FREQUENCIES OF HISTOCOMPATIBLE GENES IN THE MOUSE

Principal Investigator: Donald W. Bailey, Ph.D.

Other Investigators: Mr. John D. Andervont

Cooperating Units: None

Man Years (calendar year 1960):
Total: .6
Professional: .1
Other: .5

Project Description:

Objectives: The amount of inbreeding is usually stated in terms of the "inbreeding coefficient," which is calculated from theoretical equations taking into account the number of generations of inbreeding and the degree of relationship existing between mates. The investigators wish to ascertain here whether inbreeding effects are as predicted by theory, by analyzing what changes are taking place at the histocompatible loci.

Methods Employed: The investigators are maintaining 12 inbred lines that have originated from the same double-hybrid cross and that have been full-sib mated for 18 generations. These will be analyzed by a series of graft exchanges made within

Part A (Cont'd)

lines. From the percentage of surviving grafts in each line an estimate can be made of the number of loci that are still segregating. A similar exchange of grafts at the 22nd and later generations, will enable a determination as to whether the number of loci that still show segregation are reduced as predicted by theory.

Major Findings: The investigators are now in the process of collecting adequate numbers of offspring in the 19th generation for carrying out the proposed series of graft exchanges. No major findings have developed.

Significance: Mouse geneticists have taken the 20th generation of full-sib mating as the point at which to declare a strain to "inbred strain" in full status, for, according to theory, 99.3 percent of the originally segregating loci will have become homozygous by then. However, if forces other than inbreeding are important, such as natural selection favoring the heterozygote, then this estimated degree of homozygosity may be in great error. Observations to be made on the histocompatibility loci should provide some evidence on this point. Since much research is based upon the assumed genetic homogeneity of inbred mouse strains, it is deemed important to ascertain the degree to which this assumption holds.

Proposed Course of Project: It is the intention to terminate this project as soon as the majority of lines become totally homozygous at the histocompatibility loci.

Part B included Yes X No____

(ATTACHMENT I)

Serial No. 4.18

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications

Publications:

Bailey, D. W., and Usama, B. A rapid method of grafting skin on tails of mice. Transplantation Bulletin, 7: 424-425, 1960.

Honors and Awards related to this project:

None

(ATTACHMENT I)

Serial No. 4.19
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: A STUDY OF THE GROSS AND HISTOPATHOLOGICAL CHARACTERISTICS OF THE DISEASES OF RHESUS MONKEYS BEFORE, DURING AND FOLLOWING TRANSPORT FROM INDIA TO U.S.A.

Principal Investigators: Anton M. Allen, D.V.M.
Roy F. Kinard, D.V.M.

Other Investigators: None

Cooperating Units: Parke, Davis & Co., Detroit; Christ Hospital Institute of Medical Research, Cincinnati; Animal Hospital Section, NIH

Man Years (calendar year 1960):
Total: .41
Professional: .08 (Allen and Kinard)
Other: .33 (Meggers, Moore, Faulkner's tissue unit)

Project Description: This is a part of a study of the diseases of rhesus monkeys, sponsored and directed by the National Advisory Committee on Primates.

Objectives: To determine the presence of anatomical and histological lesions in rhesus monkeys which die before, during and following transport to U.S.; and to correlate these findings with the environmental factors and the results of the microbiological studies.

Part A (Cont'd)

Methods Employed: Six hundred fifty-two monkeys were purchased and identified in India and transported to the U.S.A. by air. The survivors of the journey were divided among three research institutions, one of which is NIH. Autopsies were performed on all the monkeys which died. Tissues taken at autopsy at the three institutions are being examined microscopically by the Comparative Pathology Section, NIH.

Concurrently, other investigators at the three institutions are attempting to isolate and identify viral, bacterial and parasitological agents and to evaluate the environmental factors which may lead to illness and death.

Major Findings: Summary of the lesions observed at autopsies of monkeys of the NIH group:

Total autopsies	63
Pulmonary consolidation	33
Pleurisy	6
Pericarditis	2
Tuberculosis	3
Gastritis	2
Gastric polyps (*Noctia nocti*)	6
Enteritis	11
Colitis & Cecocolitis	26

Single instances of many other lesions have occurred.

Significance: Through increased knowledge of the etiology, pathogenesis and pathology of the diseases of rhesus monkeys before, during and following transport to U.S., losses of these monkeys can probably be reduced considerably. Such reduction in losses of monkeys will result in reduction of expense of purchase and delivery of healthy monkeys for NIH.

Part A (Cont'd)

Proposed Course of Project: The microscopic studies will continue in 1961 until completed.

Part B included Yes X No

(ATTACHMENT I)

Serial No. 4.19

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications

Publications:

None

Lectures:

Kinard, R. F. The transfer of rhesus monkeys from India to laboratories in the United States--the problems, causes of death and possible corrections. Post-graduate course on pathology of diseases of laboratory animals. Armed Forces Institute of Pathology, September 26-30, 1960.

Honors and Awards related to this project:

None

(ATTACHMENT I)

Serial No. 4.20
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: A STUDY OF THE GROSS AND HISTOPATHOLOGICAL CHARACTERISTICS OF DISEASES OF LABORATORY ANIMALS QUARANTINED BY THE ANIMAL HOSPITAL SECTION

Principal Investigators: Roy F. Kinard, D.V.M.
Anton M. Allen, D.V.M.

Other Investigators: None

Cooperating Units: Animal Hospital Section

Man Years (calendar year 1960):

Total:	3	
Professional:	1	(Kinard and Allen)
Other:	2	(Moore and Meggers, Faulkner's tissue processing unit)

Project Description:

Objective: To maintain surveillance of the causes of death of laboratory animals of the Animal Hospital Section.

To initiate and assist in disease control procedures.

To establish research projects on diseases of laboratory animals.

Part A (Cont'd)

Methods Employed: Ordinary autopsy and histopathology methods are employed. Certain animals that die during quarantine are selected by the animal hospital staff and submitted for autopsy.

Cooperate with the Animal Hospital in initiating disease control measures and research projects.

Major Findings: Results of autopsies by animal categories:

Monkeys	114 Autopsies
Intestinal inflammation occurred in	18%
Tuberculosis occurred in	30%
Pneumonia occurred in	11%
A limited number of autopsies of New World monkeys (squirrel and marmoset) revealed:	
Thorny head worms (Prosthenorchis) in ileum	50%
Microfilaria in blood	50%
Dogs	48 Autopsies
Gastroenteritis occurred in	12%
Bronchopneumonia occurred in	6%
Nephritis occurred in	12%
Prostatitis occurred in	6%
Distemper occurred in	10%
Neoplasms occurred in	48%
Cats	18 Autopsies
Panleukopenia occurred in	53%
Respiratory inflammation occurred in	20%
Neoplasms occurred in	10%
Farm Animals	7 Autopsies

Many other lesions were found, each in insignificant percentage.

Part A (Cont'd)

Maintenance of the primate tuberculosis control program has depended upon results of autopsies of tuberculin tested animals.

Dogs vaccinated in the distemper control program have shown evidence of distemper on autopsy.

Panleukopenia has been found in cats vaccinated with certain types of vaccine.

Research projects on specific disease problems have been initiated as a result of autopsy findings: (a) Study of filariasis in laboratory animals; (b) an attempt to determine the percentage of dogs with clinical distemper that show histopathological evidence of distemper.

Significance: Surveillance of diseases of the laboratory animals of the large NIH colonies is necessary to detect and control disease outbreaks.

Knowledge of the lesions of animals dying in the Animal Hospital Section improves the ability of the hospital clinicians to diagnose and control the diseases of the animals under their care.

Correlation of clinical, laboratory, and postmortem findings aids in the thorough understanding of diseases of laboratory animals.

Histopathology findings provide basis for the initiation and performance of research on animal diseases.

Proposed Course of Project: Continuation, with considerable emphasis being placed on development of intensified studies of certain aspects of animal diseases.

Part B included Yes X No

(ATTACHMENT I)

Serial No. 4.20

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications

Publications:

Allen, A. M. Occurrence of the nematode, Anatrichosoma cutaneum, in the nasal mucosa of Macaca mulatta monkeys. American Journal of Veterinary Research, 21: 389-392, 1960.

Kinard, R. F., and McPherson, C. W. The use of trichloroethylene and halothane anesthesia in the restraint of laboratory primates. American Journal of Veterinary Research, 21: 385-388, 1960.

Lectures:

Allen, A. M. Four internal parasites of monkeys: Nochtia nochti, Gastrodiscoides hominis, Anatrichosoma cutaneum, and Sarcocystis sp. Presented to the Helminthological Society of Washington, March 25, 1960.

Kinard, R. F. Three important parasitisms of rhesus monkeys--pulmonary acariasis, strongyloidosis, esophagostomiasis. Presented to the Helminthological Society of Washington, March 25, 1960.

Kinard, R. F. Dysentery, tuberculosis and pneumonia of rhesus monkeys. CO-STEP seminar, NIH, August, 1960.

Honors and Awards related to this project:

None

(ATTACHMENT I)

Serial No. 4.21
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: A STUDY OF THE NATURALLY OCCURRING DISEASES OF LABORATORY ANIMALS

Principal Investigator: Robert T. Habermann, D.V.M.

Other Investigators: Rex R. Every, D.V.M.

Cooperating Units: None

Man Years (calendar year 1960):
Total: 4.5
Professional: 2
Other: 2.5 (Lewis, Talley, Faulkner's tissue unit)

Project Description: Investigations are conducted to determine the incidence and cause of the naturally occurring diseases in laboratory animals, mice, rats, guinea pigs, rabbits, hamsters, dogs, and cats, and to develop methods for the control and treatment of these diseases.

Objectives: The objectives of the project are to develop healthy, vigorous animals for research work at the National Institutes of Health; conduct investigations on bacterial, viral, mycotic, neoplastic, degenerative, and parasitic diseases, to enable research workers to distinguish between the pathology produced by the naturally occurring diseases in NIH animals; to develop effective methods for the

control or prevention of these diseases; and to develop techniques for the early recognition of outbreaks of disease in the animal colonies.

Methods Employed: Various vermicidal substances are painted on the floor, cages, and racks in animal rooms to determine the efficacy of the chemicals to control vermin.

Various insecticides are dusted on infected laboratory animals to determine the efficacy of the chemical to control external parasites.

Various anthelmintics are admixed in ground animal feed and drinking water to determine the efficacy of the chemicals in the control of internal parasites.

Various therapeutic substances are admixed in the ground animal feeds and water to determine the efficacy of the chemicals in the treatment and control of bacterial and viral diseases of laboratory animals.

Various methods of sanitation and of the care of laboratory animals are employed to determine the efficacy of these methods for controlling diseases.

Various methods and media for the isolation of the cause of disease are used to determine the efficacy of methods for the isolation of organisms.

Daily inspections of animals are conducted by attendants to remove sick and unhealthy animals so that the sources of infection are removed and a healthier colony of laboratory animals is obtained.

Investigations are carried out to determine whether bacterial, viral, or nutritional causes, or combinations of these causes are responsible for pathology observed in some of the diseases of laboratory animals.

Part A (Cont'd)

Daily parasitic, bacteriologic, and histopathologic examinations are made of unhealthy, sick, and aged animals to determine the incidence of diseases and to detect any new diseases or spread of disease in the animal colony.

Major Findings: The major findings of this project during the past year have been:

Excellent progress has been made in a major effort to eliminate coccidiosis from the rabbit colonies of the Animal Production Section.

The control of chronic respiratory disease complex (rhinitis, middle ear infection, and endemic pneumonia) in the Sprague-Dawley strain rat nucleus, by the continuous administration of sulfamerazine in the ground rat feed.

Continued studies with sulfamerazine, oxytetracycline and tetracycline show that these chemicals are effective in the control and elimination of the chronic respiratory disease complex in rats when offered continuously in the drinking water.

Preliminary tests indicate that lindane 0.1 and 0.1 percent of malathion in talc is an effective insecticide.

That sulfaquinoxaline offered in the drinking water continuously, accompanied by good sanitary practice, is effective in the control and elimination of coccidiosis in rabbits. In association with the medication, all infected animals, as determined by the centrifugation salt flotation technique, must be immediately removed from the rabbit colony.

That methoxychlor, an ingredient in the rodent insecticide is estrogenic when dusted on weaned mice.

Proposed Course of Project: During the year the projects on infant diarrhea in mice, development of a snuffles-free rabbit colony, and the study to determine the efficacy of

Part A (Cont'd)

piperazine adepate to eliminate Passalurus ambiguus from the rabbits were stopped due to the following emergencies, which developed at the National Institutes of Health:

1. Coccidiosis outbreak in the Animal Production rabbit colonies.

2. Ectromelia in Building 5.

3. Estrogenic stimulation in weaned mice.

4. Preliminary studies to determine the relative efficacy and toxicology of malathion insecticide for mice.

The above projects will again be undertaken in 1961.

Significance: The development of healthier laboratory animals so that the experimental results are more reliable; that less animals are needed to obtain dependable experimental results, and that the cost of conducting animal experiments is reduced.

Part B included Yes X No

(ATTACHMENT I)

Serial No. 4.21

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications

Publications:

Habermann, R. T., Williams, F. P., Jr., and Fite, G. L. Occurrence of inclusion bodies in viral diseases of man and other animals, and the susceptibility of laboratory animals to some of these diseases. Journal of the American Veterinary Medical Association, 137: 161-176, 1960.

Menges, R. W., Galton, M. M., and Habermann, R. T. Cultural and serologic studies on four dogs inoculated with two Leptospiral serotypes, Leptospira pomona and Leptospira canicola. American Journal of Veterinary Research, 21: 371-376, 1960.

Honors and Awards related to this project:

None

(ATTACHMENT I)

Serial No. 4.22
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: INVESTIGATION OF THE PROBLEM OF URINARY STONES IN MICE

Principal Investigator: Roy F. Kinard, D.V.M.

Other Investigators: None

Cooperating Units: Animal Production Section
Animal Hospital Section

Man Years (calendar year 1960):
Total: .16
Professional: .08
Other: .08

Project Description:

Objectives: To describe the disease:
a. Identify and describe the stones.

b. Describe accompanying lesions.

c. Evaluate and describe methods of diagnosis.

Ascertain the etiology of the disease.

Prescribe a program for eradication.

Part A (Cont'd)

Major Findings: Clinical diagnosis by X-ray has been perfected and is in use.

The identity of the stones has been determined by qualitative chemical analysis.

The incidence of stone disease has been estimated.

Higher incidence has been found in a certain group of mice.

Significance: This disease appears to cause excessive culling of certain groups of mice. It seems likely that eradication of the ailment, or its cause, would reduce the number of mice rejected for laboratory use.

Proposed Course of Project: Continuation.

Part B included Yes_____ No__X__

(ATTACHMENT I)

Serial No. 4.23
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: CLINICAL LABORATORY EXAMINATION OF ANIMALS HELD IN QUARANTINE IN THE ANIMAL HOSPITAL

Principal Investigator: Roy F. Kinard, D.V.M.

Other Investigators: None

Cooperating Units: Animal Hospital Section

Man Years (calendar year 1960):
Total: .42
Professional: .17
Other: .25

Project Description:

Objectives: To provide clinical laboratory service to the Animal Hospital and Animal Production Sections, and to consider the needs of these sections and expand the facilities to meet the needs, so far as is practical.

To collaborate with the Animal Hospital and Animal Production Sections in research projects in which clinical laboratory procedures are required.

Methods Employed: Ordinary methods of hematology, urinalysis, clinical chemistry, parasitology, and mycology have been used during 1960.

Part A (Cont'd)

Major Findings: Diagnoses in individual clinical cases were more readily made and sometimes depended entirely upon laboratory findings. Several diagnoses of panleukopenia of cats were made--these diagnoses are often impossible by other means.

A preliminary survey indicated that intestinal helminth control in the dog quarantine was inadequate.

Whenever a particular disease or diagnosis became a problem, a separate project was initiated. Viral diseases of cats and urinary stones of mice are examples. Separate reports on these subjects are being submitted.

Significance: Continuous clinical laboratory service and improvement of diagnostic procedures is essential in control of disease of laboratory animals.

Proposed Course of Project: Continuation and expansion as the need arises.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.24
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: A STUDY OF THE SPREAD OF TUBERCULOSIS FROM INFECTED MONKEYS TO THEIR CAGEMATES

Principal Investigators: Roy F. Kinard, D.V.M.
Anton M. Allen, D.V.M.

Other Investigators: None

Cooperating Units: Animal Hospital Section

Man Years (calendar year 1960):
Total: .25
Professional: .08
Other: .17

Project Description:

Objectives: To determine if the standard practice of destroying the cagemates of tuberculin reactor rhesus monkeys is economical.

Methods Employed: Each rhesus monkey that reacted to tuberculin while in quarantine at the Animal Hospital was submitted for autopsy. Tissues were taken for acid-fast staining and microscopic examination for tubercle bacilli. Each cagemate to a reactor was placed under quarantine for a period of six months. Ordinarily monkeys are kept two in each cage; during the six months' quarantine, the cagemates

Part A (Cont'd)

to reactors were kept one in each cage. The cages containing the cagemates were placed in an isolated room. Each cagemate was tuberculin tested every two weeks.

Major Findings: Sixty-nine cagemates to tuberculin reactors have been placed in quarantine. Five of these reacted to tuberculin and had lesions of tuberculosis on autopsy. Four died of other causes. Sixty remained in quarantine for six months and were released for laboratory use.

Disregarding the four that died of other causes, five of sixty-five, or 7.7 percent, had tuberculosis. All five cases of tuberculosis were discovered during the first three months of quarantine. During regular quarantine of monkeys less than 2 percent are found to have tuberculosis. In view of these findings a special quarantine of three months duration for cagemates of tuberculous monkeys was put into effect.

Significance: The sixty monkeys salvaged during 1959 were valued at about $3,000. This saving may be expected each year.

Proposed Course of Project: This project is terminated.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.25
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: INVESTIGATION OF THE VIRAL DISEASE OF CATS HELD IN QUARANTINE AT THE ANIMAL HOSPITAL, NATIONAL INSTITUTES OF HEALTH

Principal Investigators: Roy F. Kinard, D.V.M.
Anton M. Allen, D.V.M.

Other Investigators: None

Cooperating Units: Animal Hospital Section

Man Years (calendar year 1960):
Total: 1.
Professional: .33
Other: .67

Project Description:

Objectives: To evaluate the diagnostic procedures and criteria for the three known important viral diseases of domestic cats, panleukopenia, pneumonitis, and rhinotracheitis.

To determine the relative importance of the viral diseases as causes of illness and death of the cats during quarantine.

Part A (Cont'd)

Methods Employed: Clinical, hematology and anatomical pathology procedures will be used to demonstrate the signs and lesions associated with the three diseases. Virology and immunology procedures are beyond our present capabilities.

Major Findings: Preliminary observations indicate that the diseases under consideration are of exceptional importance in the quarantine and conditioning of laboratory cats. The data to date are insufficient basis for any further statement.

Significance: The supply of useful cats to laboratory is menaced by viral diseases. Correct diagnosis and evaluation of these diseases is the first step toward control.

Proposed Course of Project: Continuation with highest priority.

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.26
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: FILARIASIS IN QUARANTINE LABORATORY ANIMALS

Principal Investigators: Anton M. Allen, D.V.M.
Roy F. Kinard, D.V.M.

Other Investigators: None

Cooperating Units: Animal Hospital Section

Man Years (calendar year 1960):
Total: .25
Professional: .08
Other: .17

Project Description: A study of (1) methods of identification of microfilaria, (2) the occurrence of microfilaria in dogs, marmosets, and squirrel monkeys, (3) the histochemical nature of the excretory cell and the "G cells" of microfilaria.

Objectives: To identify and determine the occurrence of microfilaria in the blood of dogs, marmosets and squirrel monkeys quarantined by the Animal Hospital Section.

To determine the occurrence of different species of microfilaria in animals from certain areas, states, or countries.

Part A (Cont'd)

To determine what factors cause the excretory cell and the "G cells" of microfilaria to stain metachromatically with the blue dyes of the basic aniline series.

Methods Employed: Microfilarial infections are revealed by routine blood examination performed by the clinical-pathology unit of the Comparative Pathology Section. The microfilaria are identified on the basis of morphological differences, circulatory periodicity, and identification of adult Filaria whenever possible. The source of the animals is determined from the Animal Hospital records. Specific histochemical methods are employed to reveal the position of the excretory cell and the "G cells" of the microfilaria and provide evidence of their chemical composition.

Major Findings: Early findings suggest that the microfilaria of dogs are primarily those of Dirofilaria immitus, and the microfilaria of marmosets and squirrel monkeys are those of Dipetylanema Spp.

Preliminary studies indicate that the excretory cell and "G cells" of microfilaria may be demonstrated more clearly with methyl green and pyronin than with the commonly used blue basic dyes.

Significance: The animals under study are issued to laboratories to be used for research purposes. It is, therefore, highly desirable that diseases affecting these animals be identified and that the nature of the diseases be carefully studied.

Proposed Course of Project: Continuation

Part B included Yes_____ No X

(ATTACHMENT I)

Serial No. 4.27
1. Laboratory Aids Branch
2. Media & Glassware Preparation Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: FLUORESCEIN AMINE MEDIA FOR RAPID DIFFERENTIATION OF STAPHYLOCOCCI

Principal Investigator: Alexander Kimler, Ph.D.

Other Investigators: None

Cooperating Units: Employee Health Office

Man Years (calendar year 1960):
Total: .20
Professional: .15
Other: .05

Project Description: By incorporating mannitol and fluorescein amine in a number of media, it was found that fermentation of the sugar correlated with colony fluorescence of Staphylococcus aureus.

Part B included Yes____ No X

December 1960 Calendar Year 1960

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS 5
Serial Number

2. Computation & Data Processing Branch
Branch

3. Dr. Norman Z. Shapiro
Branch Chief

Objectives

The objectives of the Computation and Data Processing Branch are:

To provide expert mathematical and statistical consulting in the design, execution, and analysis of experiments and studies.

To plan and conduct research in the application of mathematics, statistics, and data processing methods to bio-medical investigations.

To provide a central data processing service consisting of electronic computing and electric accounting machinery.

Programs

The program of this Branch is to carry on the above objectives. Its activities continue from year to year and are financed through the NIH Service and Supply Fund. These activities to date are not readily classifiable by programs with a definite beginning and end. However, as staffing and equipment difficulties are eliminated, definite research programs, some currently under way on a limited scale, will be defined and developed.

Accomplishments

The Branch engages in a great deal of consultation with research investigators, biometricians, and administrative personnel in the various Institutes and Divisions, as well as with representatives of other Federal, State, and private organizations. Some of the more important projects during 1960 were:

Steps to Improve Service

Developed proposal to Surgeon General, PHS, concerning NIH acquisition of the Minneapolis-Honeywell-800 Computing System.

Developed proposal to Surgeon General, PHS, and subsequently reorganized Branch structure.

Developed proposal to Director, NIH, and subsequently acquired a Graph Scanning and Plotting System.

Consultation

Following are the more important consultation services provided by Branch staff members during the year:

Advice to the Director of NIH concerning use of data processing equipment by the Division of Research Grants.

Administrative Officer participated in a study concerned with NIH contribution to a Departmental data processing report.

Branch Chief and Administrative Officer participated in the development of PHS and NIH data processing equipment and services procurement requirements.

Chief, Operations Section, served as a Technical Expert to the Republic of Panama for the United Nations, in connection with the housing and population census for Panama.

Branch Chief was invited to serve as a member of the Advisory Committee on Computers in Research.

Chief, Operations Section, traveled to New Orleans to attend the Workshop of the End Results Group to discuss problems arising from submission of data on uniform punch cards.

Lectures - More prominent lectures given:

Branch Chief and Dr. Richard Podolsky of the Naval Medical Research Institute presented a joint paper on "Muscular Contraction: The Relation Between Kinetics and Contractile Mechanism" at the Second IBM Medical Symposium.

Branch Chief gave a lecture on data processing at the National Institutes of Health at DHEW, for the benefit of other agency representatives.

Branch Chief was guest speaker at the Biometrics Luncheon, NIH. He spoke on the Program of the Computation and Data Processing Branch.

Branch Chief was the guest speaker at the following sessions: (1) The NIAMD Photobiology Seminar on Component Analysis of Spectra, and (2) A Seminar at the National Bureau of Standards on the Theory of Computability.

Branch Chief gave a lecture to the Washington, D. C. Chapter of the Association for Computing Machinery on Computer Applications at the NIH.

Branch Chief gave a lecture on the use of computing equipment to research investigators from India.

Branch Chief was guest speaker at a Seminar held at the Bureau of Standards. His subject was "Toward an Abstract Recursive Function Theory".

Branch Chief discussed NIH's EDP facilities, particularly the IBM 650 Computer and its saturation, at the Small Meeting of Administrative Officers and Administrative Branch Chiefs.

Branch Chief was guest speaker at the National Bureau of Standards Computability Seminar. He spoke on the Classification of Degrees of Computability.

Training

The Chief, Operations Section, arranged for a class of high school students to be trained in the use of IBM machines. The classes were instructed by various members of the CDPB.

Conferences

Branch staff members participated in the following conferences:

Branch Chief participated in a conference held at NIH concerning the establishment of a nation-wide organization of groups interested in the application of digital computers to bio-medical research. This conference resulted in the founding of Biomedical Information-processing Organization with Branch Chief as president.

Branch Chief attended an organizational meeting of the Biomedical Information-processing Organization in New York during the month of December.

Branch Chief participated as a panel member in the 13th Annual Conference on Electrical Techniques in Medicine and Biology, which was held in Washington, D. C. He gave a presentation on "The Use of Computers in Medical Research at the NIH".

Branch Chief attended the Advisory Committee on Computers in Research, held at NIH.

Branch Chief chaired the NIH Data Logging Committee during which the Chief, Photobiology Section, Laboratory of Physical Biology, NIAMD, and Dr. Gentry, SA Surgeon, CO, Saint Elizabeths Hospital, NIMH, were the principal speakers.

Branch Chief and Chief, Operations Section, traveled to New York to inspect IBM installations and to discuss IBM's Medical Research Program.

Chief, Operations Section, traveled to San Francisco, California, to inspect and to discuss procedures with personnel engaged in computer activities at the Industrial Indemnity Company and the California Packing Corporation. He also visited the San Jose Plant to study the latest developments in data retrieval.

Branch Chief gave a report on the over-all situation of computer utilization and the necessity to purchase the H-800 to best serve the needs of NIH at the first meeting of the NIH CDPB Committee.

Acting Chief, Mathematical Analysis Unit and Acting Chief, Programming Unit, attended the Western Joint Computer Conference along with Administrative Officer and Branch Chief to familiarize themselves with the latest developments in Computer Equipment and EDP administration. They also discussed the possibilities of appointment with various Mathematicians, Digital Computer Programmers, and Digital Computer Analysts to the CDPB.

A panel discussion on Computer Aids to Medical Diagnosis, jointly chaired by Branch Chief and Chief, Clinical Pathology Department, was held on March 18, 1960.

Equipment Use

During the year, utilization of the IBM 650 Computer was increased to an average of 2 shifts per month. Peak utilization of 2.7 shifts occurred during the month of July. At the end of Calendar Year 1960, the relationship between research and administrative production stood at 65 per cent research to 45 per cent administrative applications. Computer utilization is expected to continue to increase during the coming months, with virtually all new applications being for the research areas. However, a significant growth in new applications is not expected, since the computing system cannot be operated above 2.5 shifts per month on a continuous basis, due to the necessity of allowing time for maintenance, reruns resulting from equipment failure or personal error, etc. A "While You Wait" telephone service was established to supply NIH personnel with instantaneous access to the capabilities of modern automatic data processing equipment. At present, the service is limited to the IBM "101".

Personnel

Intensive recruitment and training of Mathematicians, Programmers, Card Punch Operators, Console Operators, and Tabulating Equipment Operators were carried on by the Branch during the year. The over-all recruiting effort has resulted in obtaining 35 new employees. The breakdown is as follows: 11 Mathematicians, 1 Tabulation Project Planner, 1 Programmer, 11 Tabulating Machine Operators, 2 Card Punch Operators, and 9 additions to the clerical staff. Separations from the Branch during the year totaled 8, resulting in a net increase of 27 individuals, or an over-all staff increase of approximately 41 per cent.

Our training efforts have continued throughout the year and have resulted in 65 employees attending various computing, programming, and equipment operation courses sponsored by the IBM Corporation, the Minneapolis-Honeywell Corporation, or the NIH.

Major Problems

Space, personnel recruitment, training, and reorganization difficulties have been the primary problems. The renovation program following our acquisition of new space has presented severe operating problems. This program was completed by January 23, 1961, and an increase in over-all Branch efficiency is expected. Space will continue to be a major problem in the coming year, due primarily to successful recruiting and the resulting increase in equipment utilization. Recruitment efforts, through the Personnel Management Branch, have not as yet provided sufficient candidates to meet our present needs. The Branch has engaged in numerous recruiting activities during the past year, and plans to maintain the contacts which were established, and to continue its efforts in attracting qualified, professional personnel. Further extensive training in programming and equipment operation is needed to make possible the full Branch contribution to the NIH research program. Equipment changes are expected to require financial adjustments, because activities of this kind are not built into the current Service and Supply Fund rate schedule. Recommendations covering this problem are under study and will be presented in the near future.

Serial Number DRS 5.1
1. Computation and Data Processing Branch
2. Mathematical Analysis
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: CALCULATION OF TRANSIENTS IN MUSCULAR CONTRACTION

Principal Investigator: Norman Shapiro, Chief, CDPB, DRS

Other Investigators: R. J. Podolsky, Naval Medical Center, and Hermanus Vreenegoor, Acting Chief, Analysis and Programming Section

Cooperating Units: Naval Medical Research Institute, Bethesda, Maryland

Man Years: Cannot be estimated

Project Description:

Objectives:

Computer implementation of the mechanism of the muscular contraction under the various hypotheses.

Method Employed:

Conventional mathematics, Monte Carlo techniques and experimental programming techniques.

Part B included Yes_____ No X

Major Findings:

Complex molecular level models of biological systems can successfully be employed by means of digital computer techniques, related to those used in atomic physics and military technology.

Significance to Bio-Medical Research:

The ability to employ models of biological systems by means of digital computers should prove to be powerful investigative tools in many bio-medical areas.

Proposed Course of Project: Continue work

Serial Number DRS 5.2
1. Computation and Data Processing Branch
2. Mathematical Analysis
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

rt A.

Project Title: THE KINETICS OF CHEMICAL REACTION OF MIGRATORY SYSTEMS

Prinicpal Investigator: Norman Shapiro, Chief, CDPB, DRS

Other Investigators: None as yet

Cooperating Units: None as yet

Man Years: Cannot be estimated

Project Description:

Objectives:

The formulation of a mathematical system which will allow the analysis of systems of chemical reactions which occur in conjunction with the migration of reacting species.

Method Employed:

Partial differential equations, digital computer techniques, and linear vector algebra.

Part B included Yes_____ No X

Major Findings:

By means of appropriate linear transformations, the partial differential equations covering these types of reaction systems may be simplified to a form which allows digital computer solution.

Significance to Bio-Medical Research:

The techniques developed here promise to supply laboratory research with more powerful methods for interpreting the results of experimentation for employing such techniques as electrophoresis, chromatography, and centrifugal techniques.

Proposed Course of Project:

Obtain collaboration of laboratory investigators in order to test the applicability of these methods to actual laboratory data.

Serial Number DRS 5.3
1. Computation and Data Processing Branch
2. Mathematical Analysis
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: STUDIES OF THE MATHEMATICAL FOUNDATIONS OF THEORIES OF COLOR VISION

Principal Investigator: Norman Shapiro, Chief, CDPB, DRS and Rosalind B. Marimont, NIMH

Other Investigators: None

Cooperating Units: Computation and Data Processing Branch, Division of Research Services, NIH, and Office of Director of Basic Research, National Institute of Mental Health, NIH

Man Years: Cannot be estimated

Project Description:

Objectives:

The mathematical analysis of the relationship between empirical evidence and various theories of color vision.

Method Employed: Hilbert Space Theory

Part B included Yes____ No X

Major Findings:

The plausibility of the multi-receptor theory of color vision is a consequence of less experimental evidence than was hitherto realized.

Significance to Bio-Medical Research:

It is believed that these results can be also made to apply to the types of sensory perception.

Proposed Course of Project: Continue work

Serial Number DRS 5.4
1. Computation and Data Processing Branch
2. Mathematical Analysis
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: NONLINEAR LEAST SQUARES FITTING

Principal Investigator: Norman Shapiro, Chief, CDPB, DRS

Other Investigators: None

Cooperating Units: Biometrics Research Branch, National Heart Institute, NIH, Biometrics Branch, National Institute of Mental Health, NIH, and Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases, NIH

Man Years: Cannot be estimated

Project Description:

Objectives:

The development of a digital computer technique for fitting functions with nonlinear parameters to empirical data.

Method Employed: Numerical Analysis

Part B included Yes_____ No X

Major Findings: None as yet

Significance to Bio-Medical Research:

This technique, when successfully developed, will be applicable to the statistical study of various physiological processes, such as work in drug kinetics, as well as to the analysis of the results of laboratory experiments such as spectroscopy.

Proposed Course of Project: Continue work

Calendar Year 1960

Summary of Branch Activities

1. DRS-6
Serial Number

2. SANITARY ENGINEERING BRANCH
Branch

3. William B. Page, San. Engr. Dir.
Branch Chief

Objectives

The Sanitary Engineering Branch provides services, consultation and special studies to the Institutes and Divisions of NIH to maintain, improve and develop satisfactory conditions of environmental health.

Programs

Environmental Health Section

This Section maintains a continuous sanitary surveillance of facilities and services relating to patient and employee environmental health, including water supply for patients and employees, food services and concessions, waste handling and disposal, plant housekeeping and maintenance, hospital and employee contamination hazards, and industrial hygiene problems such as toxic fumes, irritants, air pollution, sound and vibration control, ultraviolet light, and odor control.

It reviews plans for new construction and alterations and identifies and recommends corrections to environmental health defects in existing buildings.

It conducts special studies in environmental health problems including hospital and laboratory contamination, sound and vibration controls, air pollution, cross-circuiting of laboratory fumes, odor control, water supply, and dry or wet waste disposal.

Insect and Rodent Control Section

The objective of the Insect and Rodent Control Section is the elimination and prevention of insect and rodent infestation at NIH by regularly scheduled insecticidal application and the maintenance of rodent traps and poison bait stations. In addition, it studies insecticide techniques to improve the control of the gross factors at NIH which encourage the presence and reproduction of insects and rodents.

Equipment Testing and Quality Control Section

The objective of this Section is to maintain and improve the quality of

materials and performance of equipment connected with such functions as distilling and deionizing of water, cleaning of laboratory glassware and animal cages, sterilizing laboratory and hospital materials, and protection of equipment from corrosion. It also reviews laboratory layout plans and designs and supervises the installation of laboratory equipment in field stations or special laboratories.

This section tests and develops new devices and processes for cleaning, disinfecting and sterilization of materials and equipment as related to medical research facilities. It provides quality control for the stills and deionized water, detergents, animal caging equipment, sterilizers and machines for cleaning laboratory glassware, etc. It conducts special studies and provides consultation on the quality of water to be used in research, cleaning and sterilizing processes, corrosion reduction and related problems.

Germ-Free Services Section

The objective of this Section is to evaluate and control environmental conditions, prevent the occurrence of occupational and industrial diseases, develop and improve working conditions to minimize interference with research studies, and to provide engineering assistance in germfree animal technology.

It designs and develops new germfree animal techniques and equipment, with special attention to sterilization, diets and functional planning of research facilities for these purposes. It provides engineering and bacteriological control and equipment maintenance services for other germfree research personnel at NIH.

It conducts studies and investigations, reviews plans and develops design criteria to correct existing or potential environmental deficiencies. Specific problems include toxic vapors and dust, sound and vibration, waste handling, waste disposal, and hospital and laboratory hazards.

Industrial hygiene practices are stressed in this Section, as compared with sanitation and bacteriological factors which are stressed in the Environmental Health Section.

Progress and Accomplishments

ENVIRONMENTAL HEALTH SECTION

Services - Sterility Tests for Effectiveness of Sterilizers.

A total of 487 B. globigii spore strips were exposed and tested for effectiveness of various types of sterilizing other than steam, and 152 samples of residues from germfree tanks were checked during the year.

Milk and Special Formula Studies

178 samples submitted by the Nutrition Department were checked for the presence of coliform organisms.

Inspections

Quarterly inspections of the main kitchen and floor kitchens indicated a satisfactory level of sanitation in dishwashing routines. None of the 242 swabs taken from various utensils showed the presence of excessive numbers of bacteria.

Water Samples

Water samples from various areas on the reservation were taken at monthly intervals, and satisfactory bacteriological counts and chlorination levels were noted. Two taps in Building 28 showed sporadic peaks of soil organisms but no E. coli were noted.

Air Sampling

In connection with various projects on air sampling, 391 plates were exposed using various types of samplers. These included a modified Reyniers pot type sampler, the SEB modified long plate sampler, the Andersen sieve sampler and the standard fallout Petri dish plates.

Gas Sterilization

A modified oil drum was made into an ethylene oxide gas sterilizer to sterilize such items as patient toys, books, telephones, rodent traps or other types of equipment that could not be exposed to steam heat.

Consultations

This Section was in constant consultation with the Germ-Free Services Section in evaluating new methods of sterilizing germfree animal tanks, animal feed, bedding, etc. by methods of irradiation, gas or peracetic acid.

Consultation was provided for the control of mold growth in the cold rooms in Building 29 and on the bacteriological quality of the air in the air conditioning system in this building. Consultation was given on the possible use of a Biogen apparatus in Building 5 on the 4th floor. No permanent solution was agreed upon for this problem.

Consultation was given to various groups interested in the new surgical wing ventilation system testing program.

On a trip to the University of Minnesota members of the School of Public Health there demonstrated their methods of air sampling and study.

Special Studies

The study on staphylococci in the Clinical Center was continued from the previous year. Routine air samples were taken in the various operating suites, and the total numbers of bacteria were found to depend directly on the number of individuals in the room at the time of the sampling. The total numbers of bacteria varied from 2 to 16 per cubic foot during surgical procedures,

but S. aureus coagulase positive colonies were rarely noted in either the fallout or the slit sampler plates.

In order to enumerate the coagulase positive staphylococci on swabs from floors, instruments, skin areas, noses, etc., a selected egg yolk media was developed which makes it possible to identify about 85% of the coagulase positive staphylococci present in a swabbed or streaked culture.

Sampling of the air in the operational area of the Dental Clinics in the Clinical Center was started during the year but was not completed. These studies will be continued during 1961.

Close liaison with the housekeeping department of the Clinical Center was continued during the year and lectures to the housekeeping staff which were started in 1959 were continued during the first part of 1960. The interest exhibited by the housekeeping staff at these lectures has prompted a long-range plan for a series of scheduled training courses for housekeeping personnel conducted and organized by the sanitarian from this Section.

This Section, in cooperation with the Equipment Testing and Quality Control Section, studied the NIH laundry operations in detail and prepared a special report. Some work is needed to complete this study and this is planned for the first quarter of 1961.

INSECT AND RODENT CONTROL SECTION

Services - This Section has maintained rodent traps in all animal rooms of the Clinical Center and rodent bait stations in laboratories and animal rooms of all other buildings at NIH. It conducted routine insecticide applications in all buildings on the reservation, special insecticidal and rodenticidal services in response to specific requests, and routine inspection of animal maintenance areas, food preparation and storage areas, and laundry facilities to protect and eliminate poor sanitary practices conducive to insect and rodent infestation. It also conducted testing programs to evaluate insecticides and rodenticides for use on the NIH reservation.

A total of 523 special requests for insecticiding were serviced this year. The major pest as in years past was the German cockroach, accounting for 463 calls. Domestic flies, ants, wasps, and miscellaneous pests accounted for the remainder.

Forty-one per cent more mice were trapped in 1960 than in 1959, even though the number of trap days increased only 1.3%. This indicates improved efficiency in the trapping program. There is no accurate estimate of the number of rodents in and outside of the NIH buildings killed by the baiting program, but numerous eye witness reports of dead rodents in the construction areas were received.

The past year saw the program expanded as follows:

Rodent control operations were expanded to the new NIH farm in

Poolesville, Maryland. Both permanent and temporary rodent bait stations were placed at all construction sites on the NIH reservation and were serviced weekly during the last three months of the year. Routine insecticidal applications were expanded to Buildings 13 and 29.

Both laboratory and field evaluations of available residual insecticides were made in an attempt to select the compound to which German cockroaches at NIH are most susceptible.

The first steps were taken to develop a weekly training program for the insect and rodent controllers. Special consultative advice on the control of cockroaches, book lice, and other pests were provided to the National Library of Medicine in Washington, D.C.

EQUIPMENT TESTING AND QUALITY CONTROL SECTION

Services - Conductivity tests of the centrally distilled water were made on a daily basis in the Clinical Center and at weekly intervals in other NIH buildings, and helped to locate defects in the distilled water system so that corrective action could be taken.

Surveys of copper content in the centrally distilled and deionized water were continued, and were also used to guide the replacement of defective components in the systems.

Routine operation of water deionizers continued, although transfer of this operation in the Clinical Center to the Laboratory Aids Branch is being negotiated. The deionizer in Building 5 is being moved to Building 29 and operation of this unit will be the responsibility of the Plant Engineering Branch in the future.

New machines for washing cages and glassware, new water stills, detergents and other related materials were inspected for compliance with standard specifications.

This Section participated in cleaning and disinfecting all rooms and areas in Building 5 which contain mice, after an outbreak of Ectromelia occurred in a colony of mice there.

In collaboration with other Sections of the Branch, training lectures, demonstrations, informal talks and guided tours were presented by this Section to a variety of visitors.

Consultations

This Section provided technical assistance in the planning and installing of laboratory facilities, (laundry layout, and a Cholera ward) for the Cholera Research Laboratory in Dacca, East Pakistan. An engineer from this Section supervised the installation of equipment for the research laboratory.

Specifications were prepared for the tunnel and turntable type machines in the new Cage Washing Annex of Building 14. Functional layouts and specifications were furnished to the PEB for the new cage cleaning equipment in Buildings 6 and 8.

Special Studies

A special study of the Clinical Center distilled water system was completed in August. Recommendations were made for increasing the distilled water supply in the Clinical Center to meet anticipated increased future needs.

This Section cooperated with the Environmental Health Section in a special study of the NIH laundry operations.

GERM-FREE SERVICES SECTION

Services - During the year, 434 kilograms of diet and 62 kilograms of diet components used for germfree animals were sterilized by irradiation, a 10 per cent increase over 1959.

This Section has assisted NIAMD personnel in 63 Caesarean operations on germfree guinea pigs producing a total of 234 germfree guinea pigs, of which 73 were retained for the Germ-Free Services Section for diet studies.

Routine engineering services were provided to the users of germfree equipment in the Institutes that have germfree research laboratories. Sterilization services for germfree tanks were provided as requested, using our large sterilizer unit.

Consultations

Reports were prepared for the Air Pollution Medical Branch, Division of Special Health Services, to evaluate the ventilation and sanitation and related characteristics in the animal holding quarters operated by the University of Miami Medical School, and Wayne State University under contract with the Air Pollution Medical Branch.

Technical advice was provided to personnel at the University of Arkansas for construction of new germfree laboratory facilities.

Plans for the modifications to Buildings 5, 7, 11A, 28A, and for construction of Buildings 29, 30, 31, and 10K were reviewed for environmental health factors.

Assistance was provided NIDR for the planning of the proposed germfree area in Building 30 and in the preparation of specifications for germfree chambers to be used in the building.

Development of Engineering Design Criteria

Reports were prepared on the characteristics of Broad Run Creek, waste

water produced by kennel and cage washing equipment, and wastes produced by various research laboratory animals to develop criteria for the design of waste disposal facilities at the new NIH farm.

A report was prepared on the criteria to be used in estimating the future volume of infectious wastes to be handled at the central NIH incinerator. These criteria were needed for the design of improved can-dumping mechanisms.

Design criteria for the ventilation of animal rooms were prepared at the request of several groups outside of NIH.

In cooperation with the Instrument Engineering and Development Branch, a monitoring system prototype for continuous surveillance of germfree animal chambers is being constructed.

Occupational Health

The operation of the local incinerators in Buildings 5 and 7 was terminated, and all wastes on the NIH reservation are now transported to the central incinerator for disposal.

Special procedures were developed for handling inhalation therapy equipment after its removal from infectious patients.

Recommendations for correcting special problems in air hygiene were prepared, including an evaluation of the Clinical Center central vacuum cleaning system, preparation of specifications for biological safety cabinets, development of local ventilation procedures for toxic laboratory fumes, and an evaluation of cold room ventilation where solvents are evaporated.

The level of vibration in the vicinity of an electron microscope was studied, and corrective measures were recommended to reduce the distortion in the electron photograph.

At the request of the Clinical Center, radiation procedures were developed to sterilize catheters and mercury gauges used in surgery.

In cooperation with investigators of NIAID, NIAMD, NIDR, Walter Reed Army Medical Center, and Lobund, a germfree workshop was held for the Pathology Study Section of the Division of Research Grants.

In cooperation with the Research Facilities Planning Branch, five lectures on acoustic problems were presented to DRS personnel. Seven lectures on industrial hygiene problems were presented to the nursing attendants assigned to the Clinical Center.

Personnel Changes in the Branch

During 1960, the following personnel changes took place in the Branch: The Chief of the Environmental Health Section transferred in February, 1960, to St. Elizabeths Hospital.

One engineer was assigned to temporary duty in East Pakistan from June to December, 1960.

The senior entomologist, Chief of the Insect and Rodent Control Section, transferred to the Division of Research Grants in July, 1960.

The Chief of the Branch transferred to the RFPB for special duty in June, 1960, and a new chief arrived on duty the same month.

The Administrative Clerk retired in October, 1960.

A GS-3 clerk-typist resigned for maternity leave in October, 1960.

A WB-07 insect and rodent controller was suspended in December, 1960 and resigned January 2, 1961.

As a result of these changes new personnel have been recruited and action has been taken to reorganize the Branch. Two sanitarians have been recruited. One reported to duty in November, and a second is scheduled to report approximately December 20, 1960.

A new Administrative Clerk was recruited in October.

Two new engineers reported for duty, one in February and the other in July.

Additional clerical personnel consisting of a GS-4 clerk-typist, a GS-3 clerk-typist, and two GS-4 clerk-stenographers have been recruited.

Recruiting action is underway for an Industrial Hygienist GS-9 or Assistant Grade and an Industrial Hygiene engineer, GS-13 or Senior Grade.

Discussions have been held during the last five months of the year on the proposed reorganization of the Branch, whereby the name of the Branch would be changed to Environmental Health Branch, and two sections, Sanitation Section and Engineering Section, would form the Branch. The proposed reorganization plan will be presented to the Director's office for approval early in 1961.

Training of Personnel

Special Courses

"Noise Reduction Course" - two weeks, Massachusetts Institute of Technology, one engineer.

"Rodent Control" - two weeks, CDC, Atlanta, Georgia, one entomologist.

"Orientation in Public Health Service Sanitary Engineering" - one week, CDC, Atlanta, Georgia, two engineers.

"Instrument Servicing and Repair Workshop" - three days, New York City, one technician.

Evening Courses

Bacteriology, Modern Physics, Physical Chemistry, Mathematics, Review of Applied Engineering Sciences - three engineers, one bacteriologist, one entomologist.

Meetings

1. Third Biological Oxidation Conference, Manhattan College, New York City.

2. Central States Sewage and Waste Assocation Meeting, Madison, Wisconsin

3. Annual Meeting of Animal Care Panel, St. Louis, Missouri.

4. Annual Meeting of the National Pest Control Association, Tulsa, Oklahoma.

5. International Nutrition Conference, Washington, D. C.

6. Society of American Bacteriologists, Philadelphia, Pennsylvania.

7. Society for Industrial Microbiology, Stillwater, Oklahoma.

8. Conference on Anti-Microbial Agents, Washington, D. C.

9. Institute on Laundry Management and Operation of the American Hospital Association, Chicago, Illinois.

10. Advanced Institute on Hospital Housekeeping of the American Hospital Association, New York City.

11. Seminar on Environmental Aspects of Institutional Infections, CDC, Atlanta, Georgia.

12. Training Lecture, 457th General Hospital, USARC, Baltimore, Maryland.

Special Visits to Obtain Technical Information

1. Technical Development Laboratories, CDC, Savannah, Georgia.

2. Lobund Institute, University of Notre Dame.

3. Bioengineering Department, Georgia Institute of Technology.

4. Division of Environmental Health and Safety, University of Minnesota.

5. Seimonson Laboratories, Minneapolis, Minnesota.

6. Darrow Laboratories, Inc., Brooklyn, New York.

7. Charles River Breeding Laboratories, Inc., Brookline, Massachusetts.

8. Carworth Farms, Inc., New City, New York.

9. S and E Farms, Kingston, New York.

10. Protection Branch, U. S. Army Chemical Corps, Biological Laboratory, Fort Detrick, Maryland.

11. Industrial Systems Company, Matawan, New Jersey.

12. Metalwash Machinery Company, Elizabeth, New Jersey.

Publications in the Branch

1. "Cage and Kennel Wastes in a Colony of 140,000 Laboratory Animals", prepared by Mr. Jaworski and Mr. Hickey is being cleared for publication in the Journal of Water Pollution Control Federation.

2. "Environmental Health Needs for Hospitals and Medical Centers", prepared in collaboration with representatives from CDC and NIH for presentation at the annual APHA meeting in San Francisco, California.

3. "Instrumentation for an Equipment Testing and Quality Control Program in a Medical Research Facility", by Mr. Harry Stierli for presentation at the Regional Meeting of the Instrument Society of America, St. Louis, Missouri, January 17, 1961.

4. "A Medium for the Isolation and Identification of Coagulase-Positive Staphylococci", by Lloyd G. Herman and Frank A. Morelli, presented to the meeting of the Society of American Bacteriologists in Philadelphia, Pennsylvania, in May, 1960.

5. "A Study of Problems in the Prevention and Control of Staphylococcus in the Hospital Laundry Environment", by Lloyd G. Herman, Frank A. Morelli, Harry Stierli, and Donald G. Fox, presented at the Institute on Laundry Management and Operation of the American Hospital Assocation in Chicago, Illinois, on October 5, 1960.

6. "Opening Address to the Conference on Anti-Microbial Agents", by Lloyd G. Herman, presented at the 1960 Conference on Anti-Microbial Agents of the Society for Industrial Microbiology on October 26, 1960.

7. "The Role of the Housekeeping Department in the Control of the Staphylococcus Organism", by Lloyd G. Herman, presented at the Advanced Institute on Hospital Housekeeping of the American Hospital Assocation, New York, N. Y., on November 9, 1960.

8. "Surface Sampling Techniques and Apparatus", by Lloyd G. Herman, presented at the Seminar on Environmental Aspects of Institutional Infections at the CDC, Atlanta, Georgia, on November 21, 1960.

9. "Sepsis and Its Control in the Hospital Environment", by Lloyd G. Herman, presented at the 457th General Hospital, Turner Armory, USARC,

Baltimore, Maryland, on December 7, 1960.

Major Problems

The immediate problem facing the Branch is the shortage of space, a problem common to most of NIH. We seriously need at least semi-private and preferably private offices for the Section Chiefs to permit privacy in their consultations with members of their staff. With the staff which will be present at the end of this year we will have four or five people to a module, with the Section Chief in the same area.

A second major problem of the Branch is reorganization and realigning of the staff in agreement with the proposed reorganization. Some progress has been made along these lines in actual operating relationships, and it is believed that during a period of two or three months a total transition can be made after the reorganization has been approved.

A third major problem is the recruiting of a senior engineer with an educational background and experience in industrial hygiene to provide leadership in the occupational health and industrial hygiene problems which the Branch is called upon to identify and to solve.

Program Objectives

The program objectives of the Branch can be summarized as follows:

Environmental Health Section - the field of environmental sanitation will be strengthened with additional sanitarians. Particular emphasis will be given to training programs for the housekeeping staff, animal caretakers, laundry operators, kitchen workers and nursing aides. Emphasis will be placed on sanitation in the Clinical Center patient care areas by the assignment of a full time sanitarian with experience in hospital operation.

Sanitation standards and codes will be developed for all of the NIH buildings and facilities to provide guidance to users of these facilities in meeting the recommendations of this Branch.

Insect and Rodent Control Section - To overcome the major obstacle of resistance of insects to most of the chlorinated hydrocarbon and organic phosphate insecticides, the Insect and Rodent Control Section will continue to search for more potent insecticides which offer the least hazards to warm blooded animals and to develop more efficient methods for their application. The continued existence of poor sanitary conditions in areas of laboratory animal maintenance is conducive to high insect and rodent populations in these areas. This problem will be attacked with more intensive and thorough animal room inspections and more emphasis on corrective maintenance as a major factor in reducing the harborages of roaches and rodents. Audiovisual training programs will be conducted to aid the insect and rodent controllers in employing the latest techniques in their extermination.

Equipment Testing and Quality Control Section - Some of the operational functions in the Equipment Testing and Quality Control Section such as

regeneration of water deionizers, are being transferred to other Branches in DRS. This is intended to permit greater use of engineers for equipment testing and quality control surveillance and consultations and for laboratory equipment layouts and design.

Germ-Free Services Section - The development of a test program for evaluating ventilation patterns in the new surgical suite will be the primary problem during the first part of 1961.

A study has been started and will continue in 1961 to evaluate the air pollution problems at NIH and the best means of reducing it.

Several studies in germfree technology now underway will be continued, with particular attention to additional germfree species such as rabbits and hamsters.

A major objective of the entire Branch will be to provide to the Institutes factual reports that identify environmental health problems and recommend corrective measures for their elimination. Specifically, this means that the Branch will serve as a staff resource to provide a basis of immediate action on environmental health problems by the Institutes.

Serial No. DRS-6.1

1. Sanitary Engineering Branch
2. Equipment Testing and Quality Control Section
3. Bethesda 14, Maryland

PHS -- NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Evaluation of Gas Sterilization Equipment

Principal Investigator: Harry Stierli, Sr. San. Engineer

Other Investigators: Dr. Lloyd G. Herman, Bacteriologist, GS-12
George Elmore, Sr. Asst. San. Engineer
Norbert Jaworski, Asst. San. Engineer
Frank Morelli, Bacteriologist, GS-9
J. Paul Davies, Engineering Aid, GS-7

Cooperating Units: None

Man Years (Calendar Year 1960)

Total:	0.3
Professional:	0.2
Other:	0.1

Project Description: (See attached material)

Part B. included: Yes No

Individual Project Report

A. EVALUATION OF GAS STERILIZATION EQUIPMENT

Ojectives:

To investigate and evaluate new sterilization equipment and methods, and to determine criteria for their safe and effective use in various applications.

Methods Employed:

Small laboratory equipment ranging in size from a one-liter capacity portable unit to a large walk-in type chamber of about 425 cubic foot capacity are under study. A variety of materials and apparatus together with representative test organisms are exposed to a range of conditions to determine the effect of the gas on microorganisms and exposed materials.

Major Findings:

Non-flammable mixtures of ethylene oxide and diluent were found to be practical for sterilization of plastic germ-free chambers as well as other heat sensitive equipment and materials used in clinical and laboratory investigations.

Significance to the Program of the DRS

This study has expedited the practical application of gas sterilization methods at the NIH.

Proposed Course of Project

New gas-sterilization methods and equipment will continue to be studied.

Serial No. DRS 6.2
1. Sanitary Engineering Branch
2. Environmental Health Section
3. Bethesda 14, Maryland

PHS -- NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Evaluation of Sanitizer-Detergent Compounds for Use in Patient Areas.

Principal Investigator: Lloyd G. Herman, Ph.D.

Other Investigator: Frank A. Morelli, B.S.

Cooperating Units: Various members of the Housekeeping Staff as required.

Man Years (Calendar Year 1960)

Total: 0.25

Project Description: (See attached material)

Part B. included: Yes No

Individual Project Report

A. EVALUATION OF SANITIZER-DETERGENT COMPOUNDS FOR USE IN PATIENT AREAS

Objectives:

The use of detergent sanitizer materials has been strongly recommended for control of staphylococci in hospital environments. Since many types of these compounds are available it is necessary to define certain specifications that may enable the NIH purchasing agent to select the formula most suitable for use at the NIH.

Method Employed:

Preliminary investigation indicated that the most satisfactory test sites should involve locations close to but not actually including patient-care areas. The North Corridor of all floors of the Clinical Center would therefore fit this requirement. Various types of cleaning compounds such as soap, synthetic detergents, detergent-sanitizers, etc., were used as needed in the study. Routine cotton swabs and sterile agar media, with the required dilutions, etc., were used throughout to determine the relative contamination of 10 square inch spots.

Major Findings:

The information gathered from results to date indicate that mops and wash water play a very important function in the daily sanitation problems of a hospital. The detergent sanitizer does prevent transfer of many species of organisms from one area to another during the mopping process, but at the concentration used at present it cannot kill all organisms present on floor areas, e.g., spore formers.

Significance to the Program of the DRS:

This study is demonstrating the need for adequate equipment, materials and training to insure proper sanitation.

Proposed Course of the Project:

The study will be continued during the winter season and specifications will be established.

Serial No. DRS 6.3
1. Sanitary Engineering Branch
2. Germfree Services Section
3. Bethesda 14, Maryland

PHS -- NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: GERM-FREE SYSTEMS RESEARCH AND DEVELOPMENT

Principal Investigator: John L. S. Hickey, Sr. San. Engineer
Jan. 1 - July 1
Norbert A. Jaworski, Asst. San. Engineer
July 1 -

Cooperating Units: NIDR, NIAMD, and NIAID are cooperating in an advisory capacity in field trial evaluation of equipment developed. These institutes have no serial numbers for project.

Man Years (Calendar Year 1960)

Total:	0.4
Professional:	0.2
Other:	0.2

Project Description: (See attached material)

Part B. included: Yes No

A. GERM-FREE SYSTEMS RESEARCH AND DEVELOPMENT

Objectives:

To develop and evaluate germfree systems capable of supplying germfree animals in chambers which are conveniently transportable, easily operated, economical and adaptable to the requirements of NIH investigators.

Methods Employed:

(a) Operation and evaluation of existing types of equipment; (b) consultation with NIH investigators to determine their particular equipment needs; and (c) design, and procurement of special equipment, plus field evaluation of applicability of equipment to specific research requirements.

Major Findings:

Three small plastic isolators currently in use have proven satisfactory for short term studies and transfer operations.

Ethylene oxide has been used successfully to sterilize plastic, stainless steel and aluminum germfree chambers. This procedure is relatively simple, requires little equipment and eliminates many problems previously created by corrosive acids used for sterilization.

The need for modifications to existing equipment to increase convenience and efficiency has been demonstrated by long-term use. These are incorporated into succeeding tank designs as tank needs develop.

Significance to DRS Program:

Development of inexpensive, safe, and convenient equipment for use by research personnel is a pre-requisite to expansion of research activities utilizing germfree animals. Chambers fulfilling these criteria will eliminate the present requirement of a centralized experimental area by making available to the investigator germfree equipment and techniques which can be used in a laboratory module. Use of large isolators will be of considerable value to the Laboratory Aids Branch, DRS, as a breeding chamber for germfree animals.

Proposed Course of Project:

Extensive tests will be carried out to test the large plastic isolator developed at Notre Dame University and evaluate its applicability for breeding of germfree rats and/or mice. In conjunction with this work ethylene oxide sterilization techniques will be further tested and the use of other sterilents. (i.e. Beta Propiolactone) will be considered.

Modifications to existing equipment to suit varied and changing needs will continue as the need arises.

Part.B.

Publications:

1. Hickey, John L. S., Germfree Sanitary Engineering Presented at the 88th Annual meeting of the American Public Health Association in San Francisco.

Honors and awards relating to this project: None

Serial No. DRS 6.4
1. Sanitary Engineering Branch
2. Germfree Services Section
3. Bethesda 14, Maryland

PHS -- NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: GERMFREE GUINEA PIG DIET DEVELOPMENT

Principal Investigator: John L. S. Hickey, Sr. San. Engineer
Jan. 1 - July 1
Norbert A. Jaworski, Asst. San. Engineer
July 1 -

Other Investigators: Dr. R.E. Horton, Laboratory of Germfree Animal Research, NIAID
(NIAID Project N. NIAID-112)

Cooperating Units: Dr. H.L. Andrews, Radiation Branch, NCI
Mr. E.G. McDaniel, LNE, NIAMD

Man Years (Calendar Year 1960)

Total:	0.6
Professional:	0.2
Other:	0.4

Project Description: (See attached material)

Part B. included: Yes No

A. GERMFREE GUINEA PIG DIET DEVELOPMENT

Objectives:

To develop a nutritionally well-defined diet which will produce healthy germfree guinea pigs, with growth and other characteristics approaching those of the normal animal.

Methods Employed:

Activities during the year include: (1) further development of control techniques to insure sterility of diets (2) testing the effects of diet radiation dose on germfree animals from a nutritional and sterility standpoint and (3) development of techniques to grow germfree plants as a supplement to diets now in use.

Major Findings:

Germfree guinea pigs fed diets sterilized at 2 million rad have exhibited a more rapid growth rate than guinea pigs fed similar diets sterilized at 3 million rad. Over 440 kilograms of diet and 62 kilograms of diet components have been sterilized by irradiation during 1960 as compared to 400 kilograms of diet irradiated during 1959.

Ethylene oxide and peracetic acid have been used to sterilize bean and oat seeds in an attempt to grow germfree plants. Preliminary work indicates that it may be possible to sterilize these seeds without destroying their ability to germinate.

Significance to DRS Program:

Development of a germfree guinea pig diet which will produce guinea pigs physically and physiologically resembling their conventional counterparts will reinforce the usefulness of experimental data obtained with these animals. Such a normalizing diet would make work with germfree guinea pigs more desirable to research investigators and for proposed DRS germfree animal breeding operations.

Proposed Course of Project:

Development of a suitable germfree diet will continue with attention to: (1) effects on growth rate using diets sterilized at higher radiation dosages (2) application of radiation sterilization techniques to diets for germfree rats, mice and hamsters, (3) sterilizing diet components individually to minimize nutritional deficiencies and (4) devlopment of techniques for growing germfree plants to provide a "greens" diet for germfree animals.

PHS -- NIH
Individual Project Report
Calendar Year 1960

Part B.

Honors, awards and publications.

1. Hickey, John L. S. & Snow, Donald L.: Irradiation Sterilization of Diets for Germfree Animals, Public Works. July 1960 pp 108 etseq; Vol. 91, No. 7 July 1960

Serial No. DRS-6.5

1. Sanitary Engineering Branch
2. Environmental Health Section
3. Bethesda 14, Maryland

PHS -- NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Staphylococcus Studies (Air Contamination)

Principal Investigator: Lloyd G. Herman, Ph.D.

Other Investigator: Frank A. Morelli, B.S.

Cooperating Units: None

Man Years (Calendar Year 1960)

Total:	0.5
Professional:	0.1
Other:	0.4

Project Description: (See attached material)

Part B. included Yes No

Individual Project Report

A. STAPHYLOCOCCUS STUDIES--EVALUATION OF AIR CONTAMINATION IN SURGICAL AREAS

Objective:

To investigate and evaluate new air contamination measuring devices and methods and to determine safe and dangerous levels in specific areas.

Methods Employed:

Several available types of equipment have been obtained and are being studied under varying conditions. The machines used in the study include:

1. New Reyniers pot Type slit sampler
2. New Fort Detrick type long slit sampler
3. Andersen sieve sampler
4. Casella slit sampler.

Major Findings:

When properly adjusted and operated the above instruments can be used to determine the relative density and general types of viable organisms present in air in any given location. The emphasis is, of course, on the presence of Staphylococcus aureus, hemolytic and coagulase-positive cells. Very few samples were positive for S. aureus and of these the total coagulase-positive count was likewise very low, less than 1% of the colonies growing on any one plate. The majority of organisms found in operating rooms, cleaned and with filtered air circulation, were released by the patient and staff members.

Significance to the Program of DRS:

This study has revealed the circulating air to be a minor source of S. aureus, but when staphylococci are distributed by carriers or patients with known infections they can be isolated from the air surrounding these persons.

Proposed Course of Project:

The present tests are being continued and studies will be expandedd as soon as the new surgical wing becomes available.

Serial No. DRS 6.9
1. Sanitary Engineering Branch
2. Germfree Services Section
3. Bethesda 14, Maryland

PHS -- NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: THE EFFECTS OF VENTILATION AND OTHER VARIABLES ON THE BACTERIOLOGICAL QUALITY OF AIR AT THE SURGICAL WOUND SITE

Principal Investigator: Harry J. Ettinger, Senior Asst. San. Engineer, Germfree Services Section, SEB

Other Investigator: Dr. L. G. Herman, Environmental Health Sec. SEB

Cooperating Units: Dr. Edward Laskowski, NINDB

Man Years (Calendar Year 1960)

Total:	0.1
Professional	0.1
Other:	0.0

Project Description: (See attached material)

Part B. included Yes No

A. THE EFFECTS OF VENTILATION AND OTHER PHYSICAL VARIABLES IN THE BACTERIOLOGICAL QUALITY OF AIR AT THE SURGICAL WOUND SITE

Objectives:

To study how the number of air-borne bacteria in the new Clinical Center Surgical Suite can be minimized by ventilation adjustments and use of ultra-violet light. Specifically, this study will test a new ventilation design aimed at maintaining a low level bacterial content of the air immediately surrounding the wound site. Adjunctive ultra-violet air irradiation will also be evaluated.

Methods Employed:

To date, project activity has centered on the empirical design of the ventilation system for the new Surgical Wing. Sampling to determine the bacterial content of the air in the present Clinical Center operating suite is continuing to evaluate the various factors influencing air quality in operating rooms and provide comparison data.

Major Findings:

Through consultations and review of available literature, the significant relationship of air exhaust provisions to room air quality have been established and incorporated into the design of the Surgical Wing. An adjustable air exhaust system has been provided which permits field testing to determine the most effective ventilation procedure.

Significance to DRS Program:

The design and construction of surgical facilities which offer a maximum protection for the patient against infection is of concern to DRS in its research facilities construction and maintenance program and general technological support of medical research.

Proposed Course of Project:

A test program is being developed to evaluate the several possible ventilation patterns attainable in the new surgical suite and determine which arrangement of air exhausts will minimize the bacterial concentration in the air at the wound site. Visual, chemical and contamination simulants tracer techniques will be employed. A mock up of the surgical facility to evaluate test techniques prior to field may be necessary.

December 1960 Calendar Year 1960

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities 1. DRS-7 Serial Number

2. RESEARCH FACILITIES PLANNING BRANCH 3. A. E. Williamson Branch Chief

Objectives

To plan and construct new research facilities as required by the new and expanding needs of NIH. To develop, compile and disseminate information on research facilities.

Programs

To serve as the focal point at NIH for the assembly and correlation of all information required in programing and planning the construction of all new and additional research facilities that require the participation of the Public Buildings Service, General Services Administration, and of all new and additional temporary construction of research facilities.

To provide the major contact point for coordination between the Public Buildings Service or contract architect and the appropriate NIH Institute or Division during the planning and construction of research facility until it is occupied by NIH.

To provide consultation service for the design and planning of extramural research laboratories and facilities.

Progress and Accomplishments

During the year, the branch was designated to act as the architectural and engineering resource agency for NIH, as a result of an urgent need for support in the research facility construction field. A consulting service has been organized and is available to any group or individual planning biomedical research facilities. To implement this program, a new section, the Development Section, was organized from an area formerly administered by the Design Section of the branch. The other sections of the branch are Design and Construction.

OTHER NEW DEVELOPMENTS

Intramural and Extramural Visit Programs.

Engineers of the branch visited selected laboratories on the reservation and conferred with Institute investigators for the purpose of obtaining information on laboratory requirements which will be useful in designing laboratories for new buildings at NIH and in carrying out the branch's new extramural consultation function. Contacts

have also been made with the Division of Research Grants Study Sections to obtain the names of outstanding research facilities. These facilities will be visited on a selective basis to acquire data for use in consultation.

Mock-Up Area. An area has been obtained on a temporary basis for the construction of full-size laboratory mock-ups in order to evaluate various proposed design features.

Library. The branch has established a small library to collect and catalog information regarding biomedical research and related facilities. To date, data describing newer laboratory buildings have been collected, and reports on a partition and plastic pipe study are being prepared. The library is an extension of the reference services of the NIH Library.

Personnel. Six engineers have been added to the staff for replacement of commissioned officers completing tours of duty and for expansion of consulting service in the extramural area. In order to care for the additional workload in providing information on research facilities, the administrative and secretarial staff of the branch has been increased as well.

NEW CONSTRUCTION — See attached tabulation for an itemization of new buildings under construction during 1960.

DESIGN PROJECTS — The Research Facilities Planning Branch provided technical design assistance for proposed new construction and related projects on the reservation--and elsewhere (see the first three items below).

NIH Animal Farm. Technical assistance on this project during 1960 included the preparation of a topographic survey, a master site plan, a waste feasibility study, and a program of requirements covering all facilities proposed for construction in fiscal 1962; the design of temporary dog runs, a new deep well, and a temporary water supply system; and the preliminary design for a temporary waste disposal system.

NINDB Primate Project - San Juan, Puerto Rico. Preliminary cost estimates and site investigations have been completed for this project. Uncertainties concerning final site selection have delayed any further work.

Primate Center and Station. Technical assistance was provided to the NHI Grants and Training Branch in (1) the review of plans and specifications for a primate center at Portland, Oregon, and in (2) the preparation of a suggested master site plan for a proposed primate station to be constructed at an unspecified location.

Refrigeration Plant (11-C Extension). The design of a 3330-ton combination steam turbine and steam absorption unit together with a building to house both units was completed through the Public Buildings Service on September 9.

Clinical Center Cafeteria Extension. Preliminary estimates and other required administrative material were completed in 1960, and the preparation of a program of requirements was undertaken.

Cage Washing Facilities (Building 14). Original drawings and specifications for this project were updated by Public Buildings Service preparatory to letting the construction contract early in 1961.

Revision of the NIH Master Plot Plan. Preliminary work was completed and a contract was let for updating of the Master Plot Plan for NIH buildings and grounds.

NCI Building. Preliminary cost estimates, required administrative material and a program of requirements were completed for the proposed new building.

NIMH/NINDB Building. Required administrative materials were assembled and preliminary cost estimates and a final program of requirements were completed.

Problems, Changes and Improvements

PERSONNEL — Difficulty in recruiting commissioned officers with good college records has been experienced in connection with work of the Development Section. Several prospects are now available for future assignment, but based on results of recruitment during the current year it is far from certain that commissioned personnel will be available.

OFFICE SPACE — Inadequate office space continues to be a problem and undoubtedly reduces work efficiency. A satisfactory solution to the problem would be highly desirable.

NIH AND THE PUBLIC BUILDINGS SERVICE — Some improvement has been noted in the PBS personnel and agency responsibility area. However, the lack of sufficient communication concerning construction matters still causes extreme delays in construction progress. The difficulties encountered during the preceding year in connection with the financing of building construction have improved somewhat. The continuation by RFPB, of financial accounting on the contingency items has prevented the over-obligation of funds. Informal contingency construction accounts have helped achieve financial control. However, the accounting for PBS General Office Expenses still remains unsatisfactory; the difficulty is due to the split responsibility for financial control between central and regional offices. A program is now being prepared and evaluated by PBS which is intended to consolidate financial responsibility. As an interim measure, close liaison between RFPB and the Public Buildings Service is necessary. The relationship between NIH and PBS has been improved by the assignment of an NIH budget representative to act as liaison between the branch and the Public Buildings Service. Closer liaison with the budget offices has improved financial control of construction projects.

TRAINING — Training for junior officers in RFPB is continuing on an interim plan which, hopefully, can be consolidated within calendar 1961. The use of COSTEP trainees during the summer months resulted in excellent training for under

graduate engineers and a real accomplishment in developmental work for the NIH reservation. This program will be continued.

NEW CONSTRUCTION, 1960

Building 1/	Architect	Plans Completed	Contract Awarded	Contractor	Amount	Completion Date 2/	Percent Complete
Surgical Wing (10-A)	Kiff, Colean Voss, Souder	2/4/59	6/25/59	Dean Construction Co.	$1,965,000	3/31/61	74
Power Plant 7th Compressor (11-B)	Public Buildings Service	5/15/59	7/6/59	W.G.Cornell Company	$ 217,430	7/27/60	100
Power Plant (11-C)	Nottingham Associates	9/9/60	11/28/60	W.G.Cornell Company	$1,125,000	11/28/61	1
Division of Biologics Standards Laboratory (29)	Ted Englehardt	9/27/57	2/26/58	Norair Engineering Corporation	$3,500,000	7/21/60	100
Dental Research Laboratory (30)	Ted Englehardt	10/22/58	3/25/59	Norair Engineering Corp.	$3,700,000	1/29/61	98
General Office Building (31)	Keyes, Lethbridge & Condon-Collins	5/11/59	9/4/59	Norair Engineering Corporation	$9,925,000	7/23/61	49
National Library of Medicine (38)	O'Connor and Kilham	- - - -	6/2/59	A.Venneri Company	$7,300,000	8/15/61	58

1/ Building number in parantheses.
2/ Completion date required by contract was 12/7/60, but the date estimated by PBS is 3/31/61. A supplemental construction contract will be required to complete the building for occupancy. Final completion estimated by RFPB is 9/31/61.

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

SUMMARY OF BRANCH ACTIVITIES

1. DRS-8
SERIAL NUMBER

2. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
BRANCH

3. DR. FRED ALT
BRANCH CHIEF

OBJECTIVES

TO PROVIDE THE INTRAMURAL SCIENTISTS OF THE NATIONAL INSTITUTES OF HEALTH WITH UNIQUE, NON-COMMERCIAL INSTRUMENTS AND INSTRUMENTATION SYSTEMS NEEDED FOR APPLICATION TO CLINICAL AND LABORATORY BIOMEDICAL RESEARCH;

TO PROVIDE LEADERSHIP IN THIS RAPIDLY ADVANCING FIELD, BOTH INSIDE AND OUTSIDE NIH, IN AN EFFORT TO DISSEMINATE AND OBTAIN INFORMATION ON THE LATEST DEVELOPMENTS, AND TO STIMULATE INVENTIVENESS, CREATIVENESS, AND IMPROVED PRODUCTION METHODS AND TECHNIQUES.

PROGRAMS

THE PROGRAMS OF THE BRANCH INCLUDE INVENTION, DEVELOPMENT, DESIGN, AND FABRICATION OF NON-COMMERCIAL MECHANICAL, ELECTRICAL, AND ELECTRONIC INSTRUMENTS AND APPARATUS FOR USE IN SCIENTIFIC RESEARCH AT THE NIH; MAINTENANCE AND REPAIR OF BOTH COMMERCIAL AND NON-COMMERCIAL BIOMEDICAL INSTRUMENTS; DEVELOPMENT OF NEW USES FOR THE WIDE RANGE OF AVAILABLE FABRICATING MATERIALS, AND IMPROVED PRODUCTION TECHNIQUES; AND DIRECTION OF LEADERSHIP ACTIVITIES IN THE INSTRUMENTATION FIELD, SUCH AS FOSTERING CLOSE COMMUNICATION TIES WITH OTHER BIOMEDICAL INSTRUMENTATION GROUPS, PREPARING SCIENTIFIC PAPERS FOR PUBLICATION, AND PRESENTING LECTURES ON BIOMEDICAL INSTRUMENTATION DEVELOPMENTS.

PROGRESS AND ACCOMPLISHMENTS

THE MAIN ACCOMPLISHMENTS OF THE BRANCH DURING THE YEAR LAY BOTH IN THE MANY SPECIALTY INSTRUMENTS WHICH IT PRODUCED (SUCH AS THOSE DESCRIBED IN THE INDIVIDUAL PROJECT REPORTS) AND IN THE KIND AND QUALITY OF ITS LEADERSHIP IN THE INSTRUMENTATION FIELD.

PROGRESS DURING THE YEAR, APART FROM DESIGN AND FABRICATION OF INDIVIDUAL INSTRUMENTS, CAN BEST BE MEASURED BY COMPARISON WITH THE OBJECTIVES SET AT THE BEGINNING OF THE YEAR. THE FOLLOWING WERE AMONG THE BRANCH'S MAJOR GOALS FOR 1960: ADEQUATE STAFFING TO COPE WITH THE EVER-INCREASING WORKLOAD; CLOSER CONTACT WITH RESEARCH INVESTIGATORS ON ENGINEERING AND INSTRUMENTATION; AND ENCOURAGEMENT OF ADVANCED EDUCATION IN BIOMEDICAL ENGINEERING.

ADEQUATE STAFFING TO COPE WITH THE EVER-INCREASING WORKLOAD

INSTRUMENT ENGINEERING SECTION--THE INSTRUMENT ENGINEERING SECTION WAS ABLE TO ADD TWO ELECTRONICS ENGINEERS TO ITS STAFF. THE ADDITION OF THE NEW STAFF MEMBERS HAS HELPED TO ALLEVIATE THE TREMENDOUS BACKLOG, PARTICULARLY IN ELECTRONICS PROJECTS, AT THE BEGINNING OF THE YEAR, AND HAS AIDED OUR EFFORT TO GIVE PROMPT AND HIGH-QUALITY INSTRUMENT ENGINEERING SERVICE TO NIH RESEARCH SCIENTISTS.

INSTRUMENT FABRICATION SECTION--THE GREATEST NEED FOR ADDITIONAL PERSONNEL TO COPE WITH THE INCREASING DEMAND WAS FELT IN THE FIELDS OF ELECTRONICS REPAIR AND MAINTENANCE, MINIATURIZATION, AND PLASTICS FABRICATION. BOTH THE ELECTRONICS AND MINIATURIZATION (OPTICAL) UNITS WERE ABLE TO ADD ONE MAN EACH TO THEIR STAFFS. IN THE PLASTICS FIELD, THE GREAT NUMBER OF REQUESTS FOR PLASTICS SPECIALTY FABRICATION RESULTED IN THE PURCHASE OF SPECIAL MACHINERY FOR PLASTIC MANUFACTURE AND THE HIRING OF ONE PLASTIC WORKER. A SEPARATE AREA IN THE CENTRAL SHOP WAS SET ASIDE FOR THIS WORK.

CLOSER CONTACT WITH INVESTIGATORS ON ENGINEERING AND INSTRUMENTATION

BY THE END OF 1959, AN AREA FABRICATION SHOP HAD BEEN ORGANIZED FOR THE CLINICAL NEUROPHARMACOLOGY RESEARCH CENTER, NIMH, AT ST. ELIZABETHS HOSPITAL. WHILE STRUCTURAL CONDITIONS AT THE HOSPITAL DELAYED THE MOVE OF SHOP EQUIPMENT INTO THE HOSPITAL, THE CLOSE COOPERATION BETWEEN THE RESEARCH CENTER SCIENTISTS AND THE INSTRUMENT MAKER (ASSIGNED BY THE BRANCH) PROVED MUTUALLY SATISFACTORY. PHYSICAL ESTABLISHMENT OF THE AREA SHOP AT ST. ELITZABETHS IS EXPECTED EARLY IN 1961. PLANS AND DISCUSSIONS ARE NOW UNDER WAY TO ORGANIZE A SIMILAR AREA FABRICATION SHOP FOR NIDR IN THE NEW DENTAL RESEARCH BUILDING.

A FIRST ATTEMPT TO ORGANIZE AND APPLY A MEDICO-ENGINEERING TEAM APPROACH TO RESEARCH PROBLEMS HAS PROVED EQUALLY SATISFYING. ONE ELECTRONICS ENGINEER OF THE INSTRUMENT ENGINEERING SECTION HAS BEEN ASSIGNED TO CONTINUOUS DUTY AS THE ENGINEERING MEMBER OF A RESEARCH TEAM STUDYING THE EFFECT OF HIGH FREQUENCY IRRADIATION ON BIOLOGICAL TISSUE. THE BIOLOGICAL MEMBERS OF THE TEAM BELONG TO THE SURGICAL NEUROLOGY BRANCH, NINDB. BECAUSE OF THE SUCCESS OF THE FIRST GROUP, DISCUSSIONS ARE BEING HELD WITH THE DIRECTOR OF CLINICAL RESEARCH, NINDB, ON THE POSSIBILITY OF A SIMILAR TEAM FOR OTHER RADIATION STUDIES. BOTH TEAM PROGRAMS ARE CONSIDERED LONG-TERM PROJECTS OF SEVERAL YEARS' DURATION.

Encouragement of advanced education in biomedical engineering

Efforts in this field were channelled in various directions. The most direct approach was to encourage the technical staff members of the Instrument Engineering and Development Branch to further their education in the fields of engineering and biology. This resulted in 7 persons' taking advanced training--6 at the college level and 1 in an electronic trade school. One man is engaged in premedical courses, one in postgraduate courses in both electronic engineering and physiology; the other four college students pursue engineering courses. Six of the men conduct their studies in evening courses on their own time. Three of the men receive Government subsidies for all or part of their tuition fees. Training for the one day-student, taking postgraduate courses at Stanford University, is supported under the Public Health Commissioned Officers training program.

In another effort to encourage education in biomedical engineering, the Branch has been active in fostering the development of postgraduate curricula at various universities. The Branch Chief made arrangements with Stanford University to handle an NIH instrumentation job as a thesis project, under guidance of both the University and IEDB, leading to an advanced "Electrical Engineer" degree for the Branch electronics engineer concerned. The Branch Chief conducted informal discussions on similar arrangements with the Head of the Physiology Department, Johns Hopkins Hospital, and with the Director of Medical Instrumentation, Presbyterian Hospital and Drexel Institute of Technology. One of the Branch's supervisory electronics engineers acted as Program Chairman for the conference on "Frontiers of Biomedical Engineering Education" (sponsored by AIEE, IRE, National Science Foundation, and University of Vermont) at which the needs for such training and possible curricula were discussed.

Finally, to create awareness among high school students and among scientists in other disciplines of the career opportunities in this field, an exhibit on biomedical instrumentation was prepared with the help of the Medical Arts and Photography Branch, DRS. It presents pictorially, graphically, and by descriptive text, the support given to biomedical research by the various branches of engineering. The exhibit was displayed at a national convention on medical instrumentation at Washington, D. C.; at Winston-Salem, North Carolina during National Engineers' Week; and during the Science Fair at Arlington, Virginia.

Significant Contributions to the Research Program

Intramural Research

Intramural scientists from all of the Institutes and from the Clinical Center requested the services of the Instrument Engineering and Development Branch during 1960. Instruments ranged in size from a miniaturized wireless microelectrode drive small enough to be inserted into the

SKULL OF A HIBERNATING GROUND SQUIRREL TO A LARGE SLIDE PROJECTOR DESIGNED TO PROJECT HUMAN BRAIN TISSUE SLIDES AT 94x MAGNIFICATION ONTO THE HORIZONTAL SURFACE OF A 6' DESK OR TABLE TOP. A FEW EXAMPLES OF SUCCESSFUL ENGINEERING DEVELOPMENTS, IN ADDITION TO THE MAJOR PROJECTS DISCUSSED IN THE INDIVIDUAL PROJECT REPORTS, WILL ILLUSTRATE THE WIDE RANGE OF ENGINEERING APPLICATION TO NIH RESEARCH:

A PHOTOSENSITIVE, TRANSISTORIZED DEVICE FOR DETECTING THE APPROACH OF THE MELTING POINT OF SOLID MATERIALS--THIS DEVICE RELIEVES THE INVESTIGATOR OF THE ARDUOUS TASK OF KEEPING A VIGIL ON THE SAMPLE AS IT APPROACHES ITS MELTING POINT. UPON APPROACHING THIS TEMPERATURE, THE DEVICE, SENSITIVE TO THE LIGHT TRANSMISSION CHANGES OF THE CRYSTALLINE STRUCTURE, ACTIVATES AN AUDIBLE ALARM, ALLOWING THE INVESTIGATOR TO OBSERVE THE SUBSEQUENT MELTING OF THE SAMPLE.

A DESIGN TO REDUCE THE ELECTRICAL SHOCK HAZARD OF ELECTROCAUTERY PROBES--USED IN SURGICAL OPERATIONS, THIS APPARATUS IS OF GREAT SIGNIFICANCE TO THE SAFETY OF OPERATIONS ON HUMAN BEINGS.

A MERCURY CUFF TYPE STRAIN GAUGE DEVICE--THIS IS USED BY THE SURGERY BRANCH OF THE NATIONAL HEART INSTITUTE DURING CARDIAC OPERATIONS FOR MEASURING VOLUME OUTPUT OF THE HEART. IN ORDER TO CORRELATE THIS INFORMATION WITH OTHER RECORDINGS OF THE PATIENT'S CONDITION, THE SIGNAL HAD TO BE INTRODUCED INTO A RELATIVELY HIGH IMPEDANCE AMPLIFIER. AN EXTREMELY LOW IMPEDANCE BRIDGE AMPLIFIER WAS DEVELOPED TO MATCH STRAIN GAUGE AND OUTPUT SIGNAL IMPEDANCE WITH THAT REQUIRED BY THE RECORDER AMPLIFIER.

A HOT AND COLD STIMULATOR--SENSITIVITY OF INFANTS TO HOT AND COLD TEMPERATURES IS A SUBJECT OF STUDY BY AN NIMH INVESTIGATOR. AN INSTRUMENT TO RAPIDLY ALTERNATE, CONTROL, AND MEASURE HIGH AND LOW TEMPERATURE OF A SMALL METAL SURFACE HAD TO BE DESIGNED WITH PARTICULAR ATTENTION TO ELECTRICAL AND THERMAL SAFETY. A UNIQUE HEMISPHERICAL DESIGN OF THE CONTACT PROBE ENABLES THE INVESTIGATOR TO TOUCH ONLY SMALL AREAS OF THE BODY TESTED.

AN AUTOMATIC PIPETTE PLUGGER--THIS IS USED FOR AUTOMATICALLY INSERTING RAW COTTON PLUGS INTO THE MOUTHPIECES OF STANDARD LABORATORY PIPETTES FROM 1/10 TO 10 ML. THE DEVICE REPRESENTS A STEP IN THE DIRECTION OF AUTOMATION OF RESEARCH LABORATORY PROCEDURES.

A SERIAL DILUTER--THIS WAS DESIGNED FOR THE LABORATORY OF VIRAL IMMUNOLOGY, DBS, TO MAKE SERIAL DILUTIONS OF SERUMS IN TISSUE CULTURE MEDIUM FOR THE ASSAY OF POLIOVIRUS ANTIBODIES. THE PROPORTIONALITY PATTERN OF THE VARYING DILUTIONS IS INITIALLY PROGRAMMED. UP TO 12 REPLICATE TITRATIONS CAN BE PERFORMED SIMULTANEOUSLY. THE INSTRUMENT IS APPLICABLE TO OTHER SERIAL

DILUTION TECHNIQUES, SUCH AS HEMAGGLUTINATION TITRATION AND COMPLEMENT FIXATION TITRATION.

OTHER INSTRUMENTS DESIGNED AND MANUFACTURED BY THE IEDB ARE DESCRIBED IN THE FOLLOWING ARTICLES PUBLISHED IN SCIENTIFIC JOURNALS:

A PROJECTION APPARATUS FOR HUMAN NEUROANATOMICAL RECONSTRUCTION (ANATOMICAL RECORD, MARCH 1960)

A NEW DESIGN FOR CAPTURING CAGED MONKEYS (PROCEEDINGS OF THE ANIMAL CARE PANEL, JUNE 1960)

A MULTIPLE SYRINGE BACTERIOPHAGE APPLICATOR (AMERICAN JOURNAL OF CLINICAL PATHOLOGY, MARCH 1960)

A PAPAIN DIGESTION APPARATUS (AMA ARCHIVES OF PATHOLOGY, MARCH 1960)

A NEW MICROMANIPULATOR FOR NEUROPHYSIOLOGICAL MICROELECTRODE STUDIES (JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, OCTOBER 1960)

RECENT ADVANCES IN HEART-LUNG BYPASS SYSTEMS (AIEE TRANSACTIONS, FEBRUARY 1960)

UNIVERSAL STAND WITH DRAPE RACK AND INSTRUMENT TRAYS FOR NEUROLOGICAL SURGERY (AMERICAN JOURNAL OF NURSING, NOVEMBER 1960)

MODIFIED TEST TUBE HOLDER FOR BECKMAN MODEL DU SPECTROPHOTOMETER (ACCEPTED FOR PUBLICATION IN CHEMIST-ANALYST)

PHOTOMICROGRAPHIC MICROSCOPE FOR BOTH MICRO AND MACRO APPLICATION (ACCEPTED FOR PUBLICATION IN JOURNAL OF THE OPTICAL SOCIETY OF AMERICA).

SUPPORTING ACTIVITIES FOR THE ADVANCEMENT OF INSTRUMENTATION RESEARCH:

THE INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH IS ACTIVELY ENGAGED IN FOSTERING CLOSE COMMUNICATION TIES WITH OTHER BIOMEDICAL INSTRUMENTATION GROUPS AND IN STIMULATING ACTIVITY AND RESEARCH IN THIS FIELD. IN THIS CONNECTION, THE FOLLOWING ACTIVITIES DURING 1960 ARE NOTEWORTHY:

PROFESSIONAL SOCIETY ACTIVITIES--A PROFESSIONAL INTEREST GROUP FOR BIOMEDICAL INSTRUMENTATION WAS FORMED UNDER THE CHAIRMANSHIP OF THE BRANCH CHIEF AS PART OF THE WASHINGTON CHAPTER OF THE INSTRUMENT SOCIETY OF AMERICA. THIS GROUP INCLUDES NOT ONLY PERSONNEL ENGAGED IN THE DEVELOPMENT AND DESIGN OF INSTRUMENTS

BUT ALSO THOSE INTERESTED IN THEIR MEDICAL APPLICATION AND USE. OTHER APPOINTMENTS OF IEDB STAFF MEMBERS IN PROFESSIONAL SOCIETIES CONCERNED WITH BIOMEDICAL ENGINEERING WERE:

SECRETARY OF THE JOINT EXECUTIVE COUNCIL IN MEDICINE AND BIOLOGY; MEMBER OF THE STEERING COMMITTEE OF THE FOURTH INTERNATIONAL CONFERENCE, INTERNATIONAL FEDERATION FOR MEDICAL ELECTRONICS; PROGRAM CHAIRMAN FOR THE BIOMEDICAL ACTIVITIES SESSIONS OF THE INSTRUMENT AUTOMATION CONFERENCE, INSTRUMENT SOCIETY OF AMERICA.

LECTURES AND SCIENTIFIC PAPERS--THREE LECTURES AND SCIENTIFIC PAPERS WERE PRESENTED BY IEDB STAFF MEMBERS ON INSTRUMENTATION DEVELOPED BY THIS BRANCH:

GRANT C. RIGGLE, "AN AUTOMATIC DEVICE FOR FRACTIONATION AND SPECTROPHOTOMETRIC DETERMINATION OF STEROIDS", AT THE 13TH ANNUAL CONFERENCE ON ELECTRICAL TECHNIQUES IN MEDICINE AND BIOLOGY;

DR. FRED ALT, "ELECTRICITY IN MEDICINE", AT THE JOINT MEETING OF THE WASHINGTON CHAPTERS, AMERICAN INSTITUTE OF ELECTRICAL ENGINEERS AND PROFESSIONAL GROUP FOR BIOMEDICAL ELECTRONICS, IRE;

GRANT C. RIGGLE, "INSTRUMENTATION IN BIOMEDICAL RESEARCH", AT A JOINT MEETING OF THE WASHINGTON CHAPTERS, INSTRUMENT SOCIETY OF AMERICA AND PROFESSIONAL GROUP FOR BIOMEDICAL ELECTRONICS, IRE.

GUIDED TOURS THROUGH IEDB FACILITIES--VISITING ENGINEERS AND SCIENTISTS FROM A NUMBER OF MEDICAL CENTERS CAME TO SEE THE INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH. GUIDED TOURS THROUGH THE FACILITIES WERE ARRANGED FOR THEM, AND INSTRUMENTS UNDER DEVELOPMENT WERE PRESENTED AND DISCUSSED.

ASSISTANCE TO OTHER GOVERNMENT AGENCIES--IN SEVERAL CASES, IEDB ENGINEERS AND INSTRUMENT MAKERS AIDED OTHER GOVERNMENT AGENCIES WITH RESEARCH AND CLINICAL INSTRUMENTATION. THE VETERANS ADMINISTRATION, NATIONAL BUREAU OF STANDARDS, AND NATIONAL AERONAUTICS AND SPACE AGENCY WERE AMONG THOSE REQUESTING THE BRANCH'S ASSISTANCE.

ASSISTANCE WITH DESIGN DRAWINGS AND DIAGRAMS--ENGINEERING DRAWINGS ON INSTRUMENTS DEVELOPED AND DESIGNED BY THE INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH HAVE BEEN IN DEMAND BY MANY UNIVERSITIES AND OTHER RESEARCH ORGANIZATIONS OUTSIDE NIH. A SET OF PHOTOGRAPHS OF THE IEDB HEART-LUNG MACHINE AND WIRING DIAGRAMS ON THE INSTRUMENTATION CIRCUITS FOR THE NIH CARDIAC OPERATING ROOM WERE SHOWN AT THE MEDICAL EXHIBIT IN ROME, ITALY IN THE SUMMER OF 1960.

Changes and Improvements

The year 1960 brought several improvements in the Instrument Engineering and Development Branch--mainly in organization, efficiency of operation, and quality of work output.

Organization

The establishment of the new Instrument Engineering and Development Branch in the Division of Research Services in the Spring of 1960 in place of the former Instrument Section of the Laboratory Aids Branch has made possible internal structural realignment to give proper emphasis to the growing demand for specialized kinds and quality of instrumentation service.

Efficiency

A new time and record-keeping system for the Instrument Fabrication Section went into effect this year. Designed in cooperation with the Computation and Data Processing Branch, DRS, it uses the facilities of the IBM computer for keeping of time records and material costs. It increases efficiency by freeing the technical supervisors of these purely clerical duties. It also simplifies accounting and invoicing of instrument fabrication jobs.

Quality of Work Output

The Branch has been taking initial steps in a long-term program to replace obsolete precision equipment in the Instrument Fabrication Section, almost half of which is 16 to 21 years old. Most equipment over 15 years old is obsolete for close precision tooling. This program will not only improve the quality of the work performed but will speed delivery of the end product, a factor of primary concern to the investigator.

Problems

From a long-range planning standpoint, two main problems constantly confront this Branch: Adequate training and adequate space.

Education and Training

Science and engineering have become fields of rapid change. Charged with the responsibility of providing NIH researchers with the most progressive instruments possible, the men of the Instrument Engineering and Development Branch cannot afford to rely on yesterday's knowledge, but must keep up to date with the fast-moving scientific achievements of our time. Another educational requirement is posed by the interdisciplinary character of

BIOMEDICAL INSTRUMENTATION. ITS CLOSE CONNECTION WITH BOTH THE PHYSICAL AND THE LIFE SCIENCES REQUIRES OF OUR STAFF MEMBERS A CERTAIN AMOUNT OF BASIC BIOLOGICAL KNOWLEDGE. THIS IS PARTICULARLY TRUE FOR THE ENGINEER, BUT ALSO APPLIES TO SOME DEGREE TO THE REPAIR AND MAINTENANCE TECHNICIAN SINCE INSTRUMENT REPAIRS OR MODIFICATIONS ARE OFTEN CALLED FOR BECAUSE OF BIOLOGICAL MALFUNCTION OF THE APPARATUS RATHER THAN TECHNICAL MALFUNCTION.

THE BRANCH IS MEETING THE PROBLEM OF ADEQUATE EDUCATION BY CONSTANTLY ENCOURAGING OUR TECHNICAL STAFF MEMBERS TO CONTINUE THEIR ACADEMIC TRAINING BOTH IN THEIR OWN FIELD AND IN LIFE SCIENCE SUBJECTS. IN SOME CASES, GOVERNMENT SUPPORT IS RECOMMENDED FOR EITHER STUDY TIME OR TUITION COST.

ADEQUATE SPACE

AS ADDITIONAL MACHINERY IS ACQUIRED AND ADDITIONAL PERSONNEL RECRUITED TO HANDLE THE EVER-INCREASING WORKLOAD, SPACE WILL BECOME A PROBLEM. SEVERAL STRUCTURAL CHANGES IN OUR PRESENTLY ALLOTTED AREAS HAD TO BE MADE DURING THE LAST YEAR OR ARE NOW UNDER CONSIDERATION TO ACCOMMODATE ADDITIONAL ENGINEERS AND FABRICATORS. A STUDY RECENTLY CONDUCTED BY THIS BRANCH REVEALS THAT SPACE WILL BE A MAJOR CONCERN IN EXPANSION PLANS BEYOND F. Y. 1962.

FUTURE OBJECTIVES

IN THE YEARS AHEAD, THE INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH WILL CONTINUE TO STRIVE FOR HIGH-QUALITY SERVICE TO THE NIH INTRAMURAL RESEARCH PROGRAM AND FOR LEADERSHIP IN THE FIELD OF BIOMEDICAL ENGINEERING OUTSIDE NIH. THE ESTABLISHMENT OF TEAM PROGRAMS, THE PROVIDING OF HIGHLY SPECIALIZED SERVICES, THE ESTABLISHMENT OF LOCAL AREA FABRICATION SHOPS, AND NEW SPECIALTY SHOPS SUCH AS PLASTIC, TO KEEP UP TO DATE IN THE FAST-CHANGING MATERIALS AREAS AS APPLIED TO BIOMEDICAL RESEARCH, WILL CONTINUE AS BRANCH GOALS FOR THE FUTURE. MAJOR IMPROVEMENTS WILL ALSO BE SOUGHT THROUGH THE CONTINUATION OF THE PROGRAM FOR THE REPLACEMENT OF FABRICATION MACHINERY.

THIS BRANCH WILL CONTINUE TO WORK IN CLOSE COOPERATION WITH THE RESEARCH FACILITIES PLANNING BRANCH, DRS, ON THEIR PROGRAM OF DISSEMINATING KNOWLEDGE ON BIOMEDICAL RESEARCH FACILITIES. THE OBJECTIVE OF THIS EFFORT IS TO MAKE SOME OF THE MAJOR INNOVATIONS IN MEDICAL INSTRUMENTATION DEVELOPED BY THE INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH AVAILABLE TO RESEARCHERS ALL OVER THE WORLD.

(ATTACHMENT 1)

SERIAL NO. 8.1
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. INSTRUMENT ENGINEERING SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1960

PART A.

PROJECT TITLE: THERMAL DETECTOR FOR RECOGNITION AND LOCALIZATION OF CIRCULATORY SHUNTS IN THE HUMAN HEART

PRINCIPAL INVESTIGATOR: GRANT C. RIGGLE

OTHER INVESTIGATOR: JAMES J. GILLIAM

COOPERATING UNIT: NATIONAL HEART INSTITUTE, SECTION ON CARDIOLOGY

MAN YEARS (CALENDAR YEAR 1960):
TOTAL: .2
PROFESSIONAL: .1
OTHER: .1

PROJECT DESCRIPTION:

OBJECTIVE--THE INSTRUMENT IS DESIGNED TO PROVIDE A DIAGNOSTIC TOOL FOR THE HEART SURGEON. PRESENT METHODS OF DETERMINING CIRCULATORY SHUNTS IN THE HUMAN HEART REQUIRE WITHDRAWAL OF SIGNIFICANT QUANTITIES OF BLOOD, AND CREATE PROBLEMS OF SKIN DISCOLORATION AFTER PERIODS OF TESTS. THE THERMAL DETECTOR ALLOWS DIRECT DETERMINATION INSIDE HEART CHAMBERS, THUS PERMITTING REPEATED AND EXTENSIVE INVESTIGATION, PARTICULARLY ON INFANTS AND CHILDREN.

METHODS EMPLOYED--A METHOD WAS DEVELOPED FOR ENCAPSULATING A MINIATURE THERMAL SENSING ELEMENT FOR USE DURING CATHERIZATION. A STABLE, HIGHLY SENSITIVE ELECTRONIC CIRCUIT WAS CREATED WHICH WILL DETECT THERMAL CHANGES IN THE ORDER OF .005°C CAUSED BY THE INTRODUCTION OF SALINE BELOW BLOOD TEMPERATURE. CIRCULATORY SHUNTS IN THE HEART ARE DETECTED BY MEASURING THE TIME INTERVAL BETWEEN THE APPEARANCE OF THE TEMPERATURE DROP IN THE VARIOUS HEART CHAMBERS. BY INSERTING THE THERMAL SENSING ELEMENTS IN DIFFERENT CHAMBERS OF THE HEART

AND THE BLOOD STREAM, THE EXACT LOCATION OF THE SHUNT WITHIN THE HEART CAN BE DETERMINED BY COMPARISON WITH THE TIME LAPSE UNDER NORMAL CONDITIONS.

SIGNIFICANCE TO BIOMEDICAL RESEARCH--THE INSTRUMENT MAKES POSSIBLE A NEW METHOD OF DETERMINING CARDIAC SHUNTS WHICH IS HARMLESS TO THE PATIENT, HAS NO AFTEREFFECTS, AND PERMITS MORE EXTENSIVE INVESTIGATIONS THAN CURRENT METHODS.

PART B INCLUDED: YES

(ATTACHMENT 1)

SERIAL NO. 8.1

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1960

PART B. HONORS, AWARDS, AND PUBLICATIONS

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT:

THEODORE COOPER, EUGENE BRAUNWALD, GRANT C. RIGGLE, AND ANDREW G. MORROW, THERMAL DILUTION CURVES IN THE STUDY OF CIRCULATORY SHUNTS: INSTRUMENTATION AND CLINICAL APPLICATIONS. ACCEPTED FOR PUBLICATION IN THE AMERICAN JOURNAL OF CARDIOLOGY.

(ATTACHMENT 1)

SERIAL NO. 8.2
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. INSTRUMENT ENGINEERING SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1960

PART A.

PROJECT TITLE: DIRECT READING OF PERCENTAGE OF OXYGEN IN BLOOD STREAM

PRINCIPAL INVESTIGATOR: JOSEPH M. CONLON

OTHER INVESTIGATOR: GRANT C. RIGGLE

COOPERATING UNIT: NATIONAL HEART INSTITUTE, SURGERY BRANCH

MAN YEARS (CALENDAR YEAR 1960):
TOTAL: .15
PROFESSIONAL: .10
OTHER: .05

PROJECT DESCRIPTION:

OBJECTIVE--THE INSTRUMENT PROVIDES A RUGGED, PORTABLE, SMALL-SIZED, pO_2 METER FOR MEASURING THE OXYGEN ION CONCENTRATION IN THE BLOOD STREAM DURING CARDIAC OPERATIONS. IT REPLACES A COMMONLY USED NULL BALANCING INSTRUMENT WITH A DIRECT READING METER. ITS EXPANDED SCALE RANGE YIELDS GREATER ACCURACY OF MEASUREMENT.

METHODS EMPLOYED--AN AMPLIFYING CIRCUIT INCREASES THE SIGNAL OBTAINED FROM THE CLARK DETECTING ELECTRODE. THE OUTPUT IS DISPLAYED ON A DIRECT INDICATING METER. THREE SCALE RANGES CAN BE SELECTED FOR GREATER ACCURACY IN READING. COMPENSATION CIRCUITS ARE INCLUDED TO PROVIDE CORRECTION FOR TEMPERATURE, ELECTRODE, AND BATTERY VARIATIONS. THE INSTRUMENT IS HOUSED IN A SMALL METAL CABINET AND IS NOT SUBJECT TO VIBRATION OR AVERAGE ROUGH USE.

SIGNIFICANCE TO BIOMEDICAL RESEARCH--THE INSTRUMENT ENABLES THE SURGEON DURING CARDIAC OPERATIONS TO READ DIRECTLY (I.E., WITHOUT COMPUTATIONS ON HIS PART) THE

OXYGEN ION CONCENTRATION IN THE BLOOD STREAM. ONE OF ITS USES BY THE SURGERY BRANCH OF NHI IS IN CONJUNCTION WITH THE HEART-LUNG BYPASS APPARATUS DURING EXTRA-CORPOREAL BLOOD PUMPING.

PART B INCLUDED: No

SERIAL NO. 8.3
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. INSTRUMENT ENGINEERING SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1960

PART A.

PROJECT TITLE: AUTOMATIC PERFUSION APPARATUS FOR REMOVAL AND COLLECTION OF RADIOACTIVE EFFLUENTS

PRINCIPAL INVESTIGATOR: GEORGE F. NORRIS

OTHER INVESTIGATORS: GRANT C. RIGGLE, DR. NORMAN L. GERSHFELD

COOPERATING UNIT: NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, LABORATORY OF PHARMACOLOGY AND TOXICOLOGY

MAN YEARS (CALENDAR YEAR 1960):
TOTAL: .3
PROFESSIONAL: .1
OTHER: .2

PROJECT DESCRIPTION:

OBJECTIVE--THE INSTRUMENT PROVIDES A PROGRAMMED, AUTOMATIC CYCLING SYSTEM FOR THE PERFUSION OF TISSUES AND THE ELUTION AND COLLECTION OF RADIOISOTOPES FROM MUSCLE AND NERVE FIBERS.

METHODS EMPLOYED--AN ADJUSTABLE TIME-CONTROLLED MULTI-SYRINGE DRIVE SIMULTANEOUSLY EJECTS PRESELECTED QUANTITIES OF CHEMICAL INTO SIX RESERVOIR CHAMBERS TO PERFUSE SUSPENDED MUSCLE OR NERVE FIBERS. THE SOLUTION IS AGITATED BY OXYGEN OR HELIUM BUBBLING THROUGH IT. THE LIQUID THEN DRAINS INTO PLANCHETS ON AN INDEXED TURNTABLE. THE ENTIRE CYCLE IS AUTOMATIC, REPEATING ITSELF 30 TIMES AND FINALLY SHUTTING ITSELF OFF. IN ADDITION TO ITS GREATER SPEED AND ACCURACY, THE APPARATUS MINIMIZES THE HANDLING OF RADIOACTIVE EFFLUENTS BY TECHNICIANS. IT IS ESTIMATED THAT THE WORK OUTPUT OF THIS AUTOMATIC UNIT IS 6 TIMES THAT OF A SIMILAR HAND-OPERATED DEVICE.

SIGNIFICANCE TO BIOMEDICAL RESEARCH--THE APPARATUS FALLS UNDER THE CATEGORY OF INSTRUMENTS FOR THE AUTOMATION OF LABORATORY RESEARCH PROCESSES. ITS MAIN ADVANTAGE LIES IN THE ELIMINATION OF THE MANUAL HANDLING OF RADIOACTIVE EFFLUENTS BY TECHNICIANS. IT THUS REDUCES PHYSICAL DANGER TO PERSONNEL AND AT THE SAME TIME PERMITS GREATER SPEED AND ACCURACY OF OPERATION.

PART B INCLUDED: No

(ATTACHMENT 1)

SERIAL NO. 8.4
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. INSTRUMENT ENGINEERING SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1960

PART A.

PROJECT TITLE: ELECTRONIC METHOD OF CONVERTING PERCENT TRANSMISSION TO OPTICAL DENSITY

PRINCIPAL INVESTIGATOR: GRANT C. RIGGLE

OTHER INVESTIGATOR: JOHN K. CULLEN

COOPERATING UNITS: NONE

MAN YEARS (CALENDAR YEAR 1960):
TOTAL: .1
PROFESSIONAL: .1
OTHER: -

PROJECT DESCRIPTION:

OBJECTIVE--LIGHT ABSORBANCE OF A CHEMICAL MAY BE EITHER CALCULATED FROM LIGHT TRANSMISSION VALUES, EXPRESSED IN PERCENT, OR IT MAY BE EXPRESSED MATHEMATICALLY IN UNITS OF OPTICAL DENSITY. FOR MANY RESEARCH COMPUTATIONS, THE OPTICAL DENSITY UNITS ARE MORE DESIRABLE AND MORE READILY USED. THE OBJECTIVE OF THE ELECTRONIC METHOD DESCRIBED IS TO ARRIVE AT AN INSTRUMENT THAT CAN RECORD OPTICAL DENSITY ON A LINEAR SCALE FOR DIRECT READING.

METHODS EMPLOYED--ANALYSIS WAS MADE OF THE ELECTRICAL POTENTIAL OBTAINED FROM PHOTOVOLTAIC CELLS USED IN DETERMINING THE PERCENT TRANSMISSIONS OF COMPOUNDS IN CERTAIN VISIBLE LIGHT WAVELENGTHS. BY SELECTIVE ELECTRICAL LOADING OF THE CELL OUTPUT, A SIGNAL CAN BE OBTAINED WHICH IS LINEARLY PROPORTIONAL TO THE OPTICAL DENSITY OF THE SAMPLE UNDER OBSERVATION. THE APPARATUS HAS BEEN SATISFACTORILY TESTED IN A LIMITED RANGE OF VISIBLE LIGHT. TESTS ARE PLANNED TO EXTEND ITS USE THROUGH THE ENTIRE VISIBLE RANGE.

SIGNIFICANCE TO BIOMEDICAL RESEARCH--THE APPLICATION OF THE METHOD REPRESENTS A CONTRIBUTION TO BIOCHEMICAL RESEARCH IN TWO WAYS: IT ALLOWS THE SCIENTIST TO READ OPTICAL DENSITY DIRECTLY OFF THE RECORDER SCALE, AND IT AVOIDS THE MATHEMATICAL DIFFICULTIES OF THE TRANSMISSION-TO-DENSITY CONVERSION, PARTICULARLY IN THE REGION BELOW 30% TRANSMISSION. AT PRESENT THE ELECTRONIC CIRCUITRY DEVELOPED IS USED IN AN APPARATUS FOR THE ANALYSIS OF ADRENOCORTICAL STEROIDS IN URINE.

PART B INCLUDED: YES

(Attachment 1)

Serial No. 8.4

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

The description of this instrument forms part of a paper delivered at the 13th Annual Conference on Electrical Techniques in Medicine and Biology:

Grant C. Riggle, Frank O. Anderson, Laurence R. Crisp, Erich Heftmann, and David F. Johnson, Automatic Device for Fractionation and Spectrophotometric Determination of Steroids.

(ATTACHMENT 1)

SERIAL NO. 8.5
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. INSTRUMENT ENGINEERING SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1960

PART A.

PROJECT TITLE: INSTRUMENT FOR MAINTAINING PRECISE pH CONTROL OF AN ENZYMATIC REACTION (pH STAT)

PRINCIPAL INVESTIGATOR: JOSEPH M. CONLON

OTHER INVESTIGATORS: GRANT C. RIGGLE, DR. M. MURAYAMA

COOPERATING UNIT: NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, LABORATORY OF PATHOLOGY AND HISTOCHEMISTRY

MAN YEARS (CALENDAR YEAR 1960):
TOTAL: .4
PROFESSIONAL: .3
OTHER: .1

PROJECT DESCRIPTION:

OBJECTIVE--THE INSTRUMENT ALLOWS THE MAINTENANCE OF HYDROGEN ION CONCENTRATION IN AN OTHERWISE CHANGING SOLUTION AT A CONSTANT, PRESELECTED VALUE. ITS DESIGN HAD TO OVERCOME THE DIFFICULTIES POSED BY THE STEPWISE ADDITION OF THE REAGENT, THE NECESSARY ACCURACY OF THE REAGENT AMOUNT, THE TIME LAG OF THE RECORDED RESPONSE TO THE REAGENT ADDITION, ETC.

METHOD EMPLOYED--THE DEVICE CONSISTS OF A CALIBRATED HYPODERMIC SYRINGE DRIVEN BY A SERVO-AMPLIFIER MOTOR. THE SERVO SYSTEM CONTROLS THE REAGENT INPUT THROUGH FEEDBACK FROM THE pH CONTENT OF THE SOLUTION. A SPECIALLY DESIGNED ELECTRONIC SENSING CIRCUIT AND DAMPING FEEDBACK CIRCUIT ARE USED. THE QUANTITY OF REAGENT REQUIRED TO MAINTAIN THE CONSTANT pH IS RECORDED ABOVE A TIME ABSCISSA.

SIGNIFICANCE TO BIOMEDICAL RESEARCH--THE pH STAT IS USED FOR THE STUDY OF PROTEIN STRUCTURES AND AMINO ACID SEQUENCES. IT IS PRESENTLY APPLIED IN RESEARCH ON HEREDITARY ANEMIC DISEASES FOR THE INVESTIGATION OF THE MOLECULAR STRUCTURE OF HEMOGLOBIN. THE ABILITY OF THE INSTRUMENT TO MAINTAIN A CONSTANT pH LEVEL IS OF GREATEST IMPORTANCE DURING THE ENZYMIC DEGRADING OF PROTEINS, AND DURING N-TERMINAL REACTIONS OF AMINO ACIDS.

PART B INCLUDED: No

(ATTACHMENT 1)

SERIAL NO. 8.6
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. INSTRUMENT ENGINEERING SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1960

PART A.

PROJECT TITLE: PRECISION-TIMED LIGHT INTERRUPTER FOR ULTRAVIOLET ILLUMINATION OF MICROSCOPIC SPECIMENS

PRINCIPAL INVESTIGATOR: JOSEPH M. CONLON

OTHER INVESTIGATOR: NONE

COOPERATING UNIT: CLINICAL CENTER,
CLINICAL PATHOLOGY DEPARTMENT

MAN YEARS (CALENDAR YEAR 1960):
TOTAL: .35
PROFESSIONAL: .30
OTHER: .05

PROJECT DESCRIPTION:

OBJECTIVE--PHOTOGRAPHING LIVING CELLS DISPLAYED ON A TELEVISION SCREEN REQUIRES THE SPECIMEN TO BE ILLUMINATED AT A PRECISE TIME IN THE TELEVISION CAMERA CHAIN CYCLE. HERETOFORE, THERE HAS BEN NO SATISFACTORY SYSTEM OF PERFORMING THIS FUNCTION. VARIANCES IN CONTROL CIRCUITRY AND, TO A GREATER DEGREE, NON-UNIFORMITY OF PERFORMANCE OF THE ELECTRO-MECHANICAL SHUTTER WERE THE MAJOR FACTORS. THIS PROJECT WAS INITIATED TO DESIGN A SYSTEM THAT IS SUPERIOR TO EXISTING EQUIPMENT, BOTH IN SYSTEM RELIABILITY AND PRECISION AND IN THE RANGE OF TIMING ADJUSTMENT.

METHOD EMPLOYED--AN ELECTRONICALLY DRIVEN, ELECTRO-MAGNETIC SHUTTER USING A DUPLEX SYSTEM OF OPERATION IS EMPLOYED. THE ELECTROMAGNETIC SHUTTERS ARE THE VOICE COILS OF TWO ELECTRODYNAMIC SPEAKERS, EACH INDEPENDENTLY DRIVEN BY LOW IMPEDANCE TRANSISTORIZED MONO-STABLE MULTIVIBRATORS. THE SPEAKER COILS HAVE SHUTTER BLADES ATTACHED SO THAT THEY ALTERNATELY OPEN AND CLOSE THE LIGHT PATH.

SIGNIFICANCE TO BIOMEDICAL RESEARCH--THE DEVELOPMENT OF THIS SYSTEM PERMITS ACCURATE PHOTOGRAPHING, THROUGH A TELEVISION CAMERA, OF THE GROWTH RATE OF CELLS. THE DEVICE GIVES FRAME-TO-FRAME ILLUMINATION UNIFORMITY WITHIN 3%. IT IS ACCURATE FOR SHUTTER SPEEDS AS SHORT AS 1 MILLISECOND. IT IS BELIEVED THAT THE DEVICE WILL HAVE WIDESPREAD USE IN OTHER FIELDS WHERE TIME LAPSE PHOTOGRAPHY IS EMPLOYED.

PART B INCLUDED: No

(ATTACHMENT 1)

SERIAL NO. 8.7
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. INSTRUMENT ENGINEERING SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1960

PART A.

PROJECT TITLE: RADIO FREQUENCY ENERGY EFFECTS ON BIOLOGICAL MATERIALS

PRINCIPAL INVESTIGATOR: WILLIAM PEARLMAN

OTHER INVESTIGATORS: DR. M. BALDWIN, DR. J. J. ADAMKIEWICZ

COOPERATING UNIT: NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS, SURGICAL NEUROLOGY BRANCH

MAN YEARS (CALENDAR YEAR 1960):
TOTAL: 1.25
PROFESSIONAL: 1.00
OTHER: .25

PROJECT DESCRIPTION:

OBJECTIVE--THE RESEARCH PROJECT AIMS AT DETERMINING THE EFFECTS OF HIGH-DENSITY RADIO FREQUENCY IRRADIATION ON BIOLOGICAL TISSUE. THE STUDY IS CONDUCTED BY A TEAM CONSISTING OF SCIENTISTS OF THE SURGICAL NEUROLOGY BRANCH, NINDB, AND AN ELECTRONIC ENGINEER OF THE INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH, DRS. THIS REPORT COVERS THE ENGINEERING CONTRIBUTION TO THE RESEARCH PROJECT, MAINLY IN THE FIELD OF INSTRUMENTATION.

METHODS EMPLOYED--PRESENT DEVELOPMENT INCLUDES R. F. GENERATORS OPERATING FROM 220 TO 400 MEGACYCLES, PULSE MODULATORS FOR CONTROLLING DURATION OF STIMULATION, ANTENNA CAVITY RESONATORS TO MATCH FREQUENCY SPECTRUM USED, CHAMBERS FOR HOLDING MATERIAL SUBJECTED TO R. F. ENERGY, AND TECHNIQUES FOR MEASURING ABSORBED ENERGY. AS EXPERIMENTS ARE EVALUATED, NEW MEASUREMENT AND IRRADIATION STUDIES ARE UNDERTAKEN TO COVER A WIDER RANGE OF FREQUENCIES.

Significance to Biomedical Research--Higher power R. F. energies are being used in military and civilian radio and radar applications. This research project has been initiated to determine if these higher power electromagnetic energies may be harmful to biological tissue when subjected to relatively intense fields. Studies will also include possible effects on the biochemical composition of single cells.

Part B included: No

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-9
Serial Number

2. LIBRARY BRANCH
Branch

3. John J. Clopine
Branch Chief

Objectives

Branch objectives are (1) to interpret the library needs of NIH scientists and program officials, (2) to acquire, organize, maintain, and service a collection of library materials adequate to meet these needs, (3) to provide immediate access to the information required in the furtherance of biomedical research, (4) to provide professional assistance to NIH personnel in the optimum utilization of library resources, (5) to provide circulation, photocopy, and bibliographic services in the dissemination of information, (6) to provide translation services for the utilization of foreign scientific literature, (7) to provide leadership and consultative services in library-type problem areas at NIH including information storage and retrieval, (8) to investigate, plan, and initiate research for the future library needs of NIH, and (9) to care for the Library's collections through binding, replacement, reduction to microform, or withdrawal of material no longer needed.

Programs

Office of the Chief. To advise the Director, NIH, NIH scientists, officials of PHS, DHEW, and other interested biomedical research agencies, of the development and application of biomedical research information storage and retrieval techniques to the administrative and research needs of their activities; to administer the work of the NIH Library; to provide leadership, professional guidance, and consultative services in the overall development of library-type informational activities of the NIH; to investigate, plan, and initiate research for the future library needs of the NIH.

Acquisitions Section. To acquire through purchase, gift or exchange the books, journals, reports or other media designated by the Librarian as needed for the furtherance of biomedical research at NIH; to maintain a binding program for the preservation of the collections, and to dispose of material designated by the Librarian for withdrawal from the collections.

Cataloging Section. To develop cataloging procedures compatible with prompt identification and retrieval of needed information; to organize and maintain the public catalog and shelf list; to establish the entries in the Serial Record and Serial Locator files; to establish and maintain a list of subject headings reflecting the terminology and nomenclature used in biomedical

research; and to decatalog material selected for withdrawal from the collections.

Circulation Section. To establish and maintain a circulation service of library materials needed for official use by NIH personnel; to provide a photocopy service to supplement circulation service; to borrow on interlibrary loan material not available in the NIH Library; to provide stack maintenance of the collections including shelving, shelf reading, inventory, and relocation of stack areas; to provide a library pickup and delivery service to NIH buildings other than the Clinical Center; and to provide and service equipment needed for re[illegible]er utilization of microprint material.

Reference Section. To brief NIH personnel on the optimum utilization of library resources; to provide skilled assistance to the NIH investigator in the location and selection of library material; to answer telephone, mail or personal inquiries for specific information to provide bibliographic assistance upon request; and to maintain close liaison with NIH scientists and program officials to insure the Library's collections reflect their needs.

Translating Section. To provide upon request a translation service which will make available the resources of foreign biomedical literature to NIH personnel; to make these completed translations available to all interested personnel in and out of NIH within the provisions of the copyright laws; and to assist NIH officials by providing a limited interpreter service.

Progress and Accomplishments

Office of the Chief. The first draft of a proposal for branch status for the Library was completed on February 11, 1960 and approval by the Surgeon General for branch status was granted on April 20, 1960. The Library now has much greater personnel and budgetary flexibility. Branch status has also permitted direct communication with the Division offices, the integration of the Translating Section into the Library, an overall administrative reorganization of the Library, and several internal personnel changes.

To achieve greater personnel flexibility, a number of position descriptions were revised and new positions are being established to insure an orderly progression from beginning grades to senior grades in both professional and subprofessional series. Intensive efforts have been made for recruitment of qualified personnel. Contact has been established with a number of librarians who are excellent prospects once positions become available

A request for the survey of present and future library needs of the NIH was approved by the Director, NIH. Dr. Ralph R. Shaw, Dean, Graduate School of Library Service, Rutgers University was chosen to make the survey. Assisted by Mrs. Margaret Bryant, former Chief, Bibliography Division, Department of Agriculture, Dr. Shaw interviewed some 150 scientists and program officials at NIH. The final report of the survey, which is anticipated in January 1961, will be used as a basis for a reevaluation of current library policies and procedures and should provide guidelines for the future growth and development of library services.

DRS, Library Branch, cont'd:

In an attempt to analyze library user needs, the Librarian has held numerous meetings with Institute Directors, Scientific and Clinical Directors, program officials and scientists. The attitudes expressed in these meetings about library services bear close correlation with the preliminary findings of the library survey.

The statistical reporting system of the Library has been revised. Emphasis has been placed on gathering information which reports total workload, individual performance and production, costs and expenditures, and a meaningful breakdown of major categories reported.

Space needs have been analyzed and discussed with the library surveyor. Discussions have been held with the Research Facilities Planning Branch in relation to type and quantity of space needed.

The Assistant Librarian completed a major statistical questionnaire requested by the Brookings Institute for the survey of federal libraries.

Detailed budget guidelines were prepared for fiscal 1961. Internal communications within the Branch have been strengthened with provision for regular staff meetings.

Acquisition Section. In the reorganization of the Library, the Acquisition Section was formed from one part of the former Processing Unit. It retained a staff of six people. As a separate organization, it became easier to delineate functions, establish routines and assign responsibilities.

Substantive progress was made in initiating a crash binding program to alleviate the critical problem of unbound journals. Prior to the organization of the Section only 269 volumes were sent to the bindery between January 1 and May 1, 1960. From May 1 to December 1, 1960, the Section sent 6,025 volumes to the bindery, following a schedule which called for priority binding of material presenting the worst maintenance problems and material considered of greatest value to the Library.

In accordance with DHEW's program of purchasing medical books and journals through the Veterans Administration on an experimental basis, the Section placed the first NIH order in August: 570 subscriptions for 401 titles were ordered. The overall evaluation of this arrangement cannot be determined until it is seen how many problems arise in relation to receipt of the material. However, it does eliminate the costly processes of preparing invitations for bids, sending them out to dealers, comparing price quotations, etc.

Another 765 subscriptions for 705 titles were ordered by the Section through traditional procedures. Supply Management Branch has agreed to permit the Section to place the most difficult to order material on a standing order basis as orally recommended by Dr. Shaw during his survey of the Library.

Progress has been achieved in making the Serial Record more intelligible to library users who must consult it frequently and to relieve the congestion

caused by staff and public hovering over it. Binding records are being transferred to the Binding Unit and order records to the Order Unit. With this change, a system of followup on outstanding journal orders is being initiated, and records kept for material received by gift or exchange are being consolidated and simplified.

Calendar year 1960 will see the expenditure of approximately $20,000 for journals, plus about $11,000 for books and $5,500 for supplies and equipment.

Cataloging Section. The Cataloging Section was established with the reorganization of the Library. It was formerly a part of the Processing Unit. Five positions were retained in the Section.

The backlogs of material that need cataloging or recataloging have been reduced from 2,311 items in January to 1,767 on December 1. Many of these items are of low priority. Backlogs on the Preparation Desk have been eliminated. All new books received are cataloged immediately.

The monthly accession list was redesigned and given a new title, NIH Library Booklist. A list of journals currently received was compiled and published for the first time.

Circulation Section. The Section instituted a photocopy service with the acquisition of a Haloid Xerox 914 copier on October 27, 1960. The response to this service has been immediate and enthusiastic. Initial production has ranged between 800 to 1,000 copies per day.

An improved system of reporting missing books and journals to interested library staff members has been developed and is in operation.

The interlibrary loan and circulation forms were redesigned and simplified. The new forms have much greater clarity and are much easier to fill out.

Reference Section. The Reference Unit became the Reference Section. The Section has made a continuing analysis of the reference needs of NIH and the ways and means of accomplishing these needs. All reference services are now handled by the professional staff. Clerical duties are now assigned to a library assistant.

The Section prepared 27 bibliographies between January 1 and December 1. Announcements of these bibliographies appeared in the NIH Library Booklist. A total of 125 requests for previously prepared bibliographies was received between July 1 and December 1.

Individual orientations were given to 327 NIH investigators between July 1 and December 1. These orientations varied between 15 minutes and two hours.

DRS, Library Branch, cont'd:

Consultations were held with individual investigators who requested assistance on establishment of office files, methods of coding and indexing, proper publication style, journals to approach for publication, and methodology of literature research.

Several displays and exhibits were prepared by the Section. Among these were: (1) Russian journals and the corresponding English translated journal for the official USSR delegation to the NIH, (2) representative Belgian publications in the Library collection and significant holdings in nuclear science for a visit by the Belgian Ambassador, and (3) a display of journals and books of interest to visiting members of the American Hospital Association.

A library service has been established in the Research Facilities Planning Branch. A reference librarian has been recruited to survey the needs of this Branch and recommend material to be acquired, library services to be established and organization of material already on hand. An estimate of funds needed for this service is being prepared.

Translating Section. The Translating Unit became the Translating Section in May. This brought about a better integration of translating activities into the Library's activities and procedures.

In January, the Section inaugurated the practice of putting written translations on Colitho plates and making retention copies available to NIH investigators. This has substantially expanded the usefulness of the translation service with minimal increase in cost.

A survey was completed of the working tools of the translators--dictionaries. Guidelines were established for the purchase of new dictionaries. Areas where dictionary holdings are weak are being strengthened by the purchase of additional dictionaries.

A new requisition form for requests for translating service was designed to replace the obsolete form PHS-1174, originally designed for the Office of Scientific Reports. The new form will serve as a unified statistical and control form.

Equipment was procured for experimentation with recorded oral translations. Initial tests indicate that this form of translation delivered directly to the consumer will greatly speed up the translator's output.

The entire translation files of the Section were weeded and inventoried. All translations made before 1950 were withdrawn. The Card Catalog was checked to see that there were entries for all translations remaining in the files and that cards were removed for all translations no longer in the files.

Problems

Office of the Chief. Three of the major problems facing the Library are space, staffing, and budget.

Space configuration presents the greatest single obstacle to operational efficiency of the Library. The present configuration with its many exits and entrances prevents the adoption of any effective means to stop the continuing loss of books and journals. The long narrow space prevents the consolidation of collections and activities and proves very wasteful of staff time in having to walk long distances to perform their work. Location of the Library's facilities on the fifth floor of the Clinical Center is a major inconvenience to scientists located outside the building. The ideal solution would be provision of 20,000 square feet of space at ground floor level plus stack space for 100,000 volumes.

Of serious concern to library staff and patrons has been the inadequacy of funds to purchase books. Only $2,000 was spent for books between July 1 and December 1. Some alleviation of this condition is anticipated for the remainder of the fiscal year because of allocation of additional funds for this purpose. Failure to purchase new books has placed a heavy workload on the Reference and Circulation Sections and has disrupted the normal routines of the Acquisitions and Cataloging Sections.

Selection and weeding of material present additional problems. Until the present staff gains more experience and is supplemented by subject specialists, no efficient mechanism can be developed. It will soon be necessary to place as much emphasis upon weeding as is now placed upon selection.

Future planning for the Library has been largely held in abeyance until the Library Survey is received. This has kept some operations in limbo until an overall policy can be established.

Acquisitions Section. Unbound journals present a continuing problem. Assignment of two people full time will keep up with current acquisitions but will not make major inroads into the backlog. The utilization of additional personnel and the availability of additional funds will be required before the binding backlog can be cleared up.

Another major problem facing the Section is the need for a review of all procedures associated with the Section's workload. Many of these procedures have had to be revised to meet the new responsibilities of the Section without a change in number or grade of personnel assigned to the Section.

Cataloging Section. A careful review and analysis is needed for all cataloging policies and procedures. The present Card Catalog is inadequate, users have frequently protested about the vocabulary used in the subject headings, and production standards need to be set for the major work areas. This is a major undertaking and will require the concerted efforts of a highly professional staff.

DRS, Library Branch, cont'd:

Backlogs of uncataloged material remain a major problem. This material should be reviewed by the Selection Committee to determine its value to NIH.

Circulation Section. Security of the collection remains a basic problem. A multiplicity of exits and entrances to the three separate collections and unlimited access to the collections while no staff member is on duty, prevents the establishment of any feasible system of control in the space now occupied. Missing issues of journals and missing books consume more staff energy and time than any other single library problem.

Lack of adequate equipment has presented several problems in the use of microfilm and microcards by library patrons. As soon as money becomes available, microfilm and microcard readers should be purchased as well as a microfilm reader-printer. A second photocopier is needed to supplement the present photocopy service during peak demands and when the present photocopier is shut down for repairs or maintenance.

Maintenance of the collection has been inadequate. Lack of personnel has curtailed shelf reading which is a basic function of maintenance. No inventory has ever been taken of the collection. As a result, time is lost both by staff and patrons in trying to find misfiled or missing material.

Basic policies and procedures of the Section in regard to the circulation of material need to be reviewed. The present system is time consuming, cumbersome, and irksome to the borrower.

Inability to purchase books required by the Library places a severe strain upon the interlibrary loan function. Other agencies are loath to loan new material as they normally require the new material to service their own people.

Reference Section. Inability to purchase current books has curtailed the effectiveness of the reference service. New reference books, textbooks, and monographs are the lifeblood of a reference service. Curtailment of this material limits the service which can be supplied and requires undue dependence upon other agencies.

The physical layout of the Reference Section poses several problems. The placement of reference librarians behind glass partitions has produced a psychological block on the part of many investigators in asking for reference services. Attempts to relocate desks and stacks have run into considerable delay.

The establishment of a reference service in the Research Facilities Planning Branch has run into several temporary difficulties. Lack of funds for equipment, books, supplies, and journals and the lack of clerical assistance has greatly handicapped the establishment of this service

Translating Section. The large backlog of translations remains the major problem. From the requestor's standpoint, the time lag between the

placement of a request and its completion defeats the usefulness of the service. Space limitations prevent expansion of the staff. A solution seems possible based upon the following: (1) major emphasis upon oral translations which maximize the productivity of the translator; (2) portable recording equipment should be purchased to increase the flexibility of the oral program; and (3) contract services should be utilized to cover peak requests periods and to reduce accumulated backlogs.

The Section at present has minimal capability for translating English material into foreign languages. The emergence of NIH as a major participant in foreign conferences and as a contributor to foreign publications has produced a substantial need for translations into foreign languages. It might be possible to utilize the services of visiting scientists for this work.

The files of translations are indexed only by author. To be of real value, the files should be indexed by subject. This will require a major undertaking by the Cataloging Section. Cards for translations should be filed in the Public Catalog to make the translation file of optimum use to the NIH.

Space is a problem which must be solved before a really effective oral translating program can become a reality. There should be a minimum of three soundproof rooms for orals. As the program develops, there should be four or five of these rooms. Translating work requires a high degree of concentration and the present cramped quarters are not conducive to this.

Personnel

Training. Several members of the Library staff attended courses given by local universities and the U. S. Department of Agriculture Graduate School. The courses covered languages, library science, and biomedical subjects.

Recruitment. One of the major difficulties facing the Library is the recruitment of properly qualified librarians. All librarians are in short supply and those with a scientific background are at a premium. Grade structure must be revised if the NIH Library is to compete on an equal basis with other governmental libraries. The Librarian has conducted exploratory talks with a number of potential applicants, pending implementation of anticipated recommendations for staffing in the Library Survey.

Staffing. One of the major problems in the Library is the lack of qualified professional staff. Only seven members hold degrees in library science and only two members of the staff have graduate degrees in science. Of these nine people, five are spending a major portion of their time in administrative work.

Of critical importance to the Library is the development of a sound personnel program. The present library staff has accrued without any overall policy in regard to qualifications, personnel needs, grade structure, professional growth and development, training, or flexibility. It is hoped that the Library Survey will provide the guidelines for library staffing consistent with the responsibilities assigned the Library.

LIBRARY
NIH
Amazing Research.
Amazing Help.
http://nihlibrary.nih.gov

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

NIH LIBRARY
4 0107 9588

NIH LIBRARY
3 1496 00181 2539